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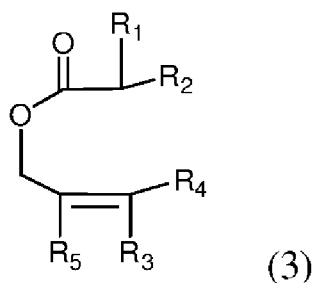
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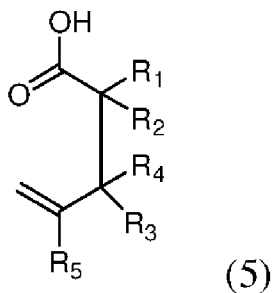
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[Continued on next page]

(54) Title: METHODS FOR PRODUCING 1-PENTANOLS, 4-PENTENOIC ACIDS, 4-PENTENOLS, AND 1-PENTANOIC ACIDS



(57) Abstract: A synthetic method includes transesterifying a carboxyl ester with a 2-propenol (i.e. 2-prop-1-ol) under conditions effective to provide a 2-propenyl ester of formula (3) and reacting the 2-propenyl ester of formula (3) under conditions effective to provide a 4-pentenoic acid of formula (5) wherein in the foregoing formulas R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ arylalkylene.





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METHODS FOR PRODUCING 1-PENTANOLS, 4-PENTENOIC ACIDS,
4-PENTENOLS, AND 1-PENTANOIC ACIDS

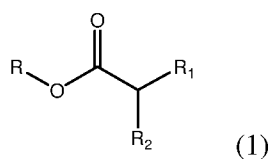
BACKGROUND

[0001] 1-Pentanol, and in particular substituted 1-pentanol are important starting materials and esterification agents used, for example, in medicinal chemistry and polymer and fine chemical production. A particular alkyl-substituted 1-pentanol is 2-ethyl-4-methyl-1-pentanol (EMPOH). Current synthetic methods for making substituted 1-pentanol such as EMPOH have various drawbacks.

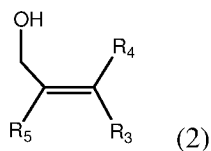
[0002] There accordingly remains a continuing need for a method for the production of 1-pentanol, in particular substituted 1-pentanol. It would further be useful if the synthetic method produced other 5-carbon intermediates or products such as 4-pentenoic acids, 4-pentenols, and 1-pentanoic acids.

SUMMARY

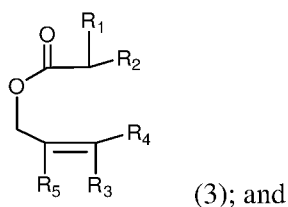
[0003] A synthetic method includes transesterifying a carboxyl ester of formula (1)



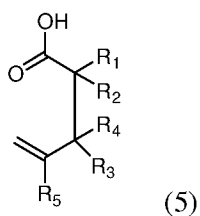
with a 2-propenol of formula (2)



under conditions effective to provide a 2-propenyl ester of formula (3)

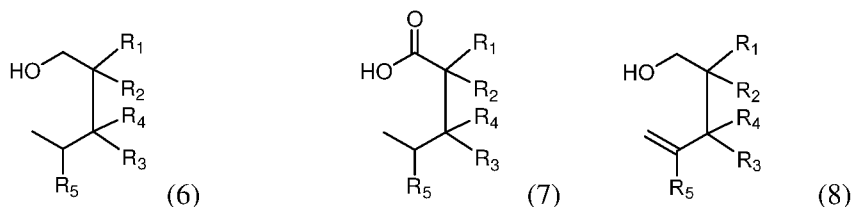


reacting the 2-propenyl ester of formula (3) under conditions effective to provide a 4-pentenoic acid of formula (5)



wherein in the foregoing formulas R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ arylalkylene, preferably wherein not all of R₁, R₂, R₃, R₄, and R₅ is hydrogen.

Also disclosed is a method further comprising reducing the 4-pentenoic acid of formula (5) under conditions effective to provide a 1-pentanol of formula (6) or the 1-pentanoic acid of formula (7) or the 4-pentenol of formula (8).



[0004] Compounds made by the foregoing methods are also disclosed, as well as compositions containing the compounds. In a specific embodiment the compound is 2-ethyl-4-methyl-1-pentanol.

[0005] The above described and other features are exemplified by the following Detailed Description.

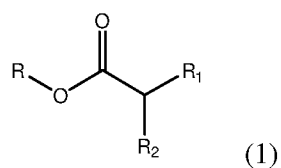
DETAILED DESCRIPTION

[0006] Described herein is method for producing 1-pentanol, their corresponding 4-pentenoic acid precursors, 1-pentanoic acids, and 4-pentenols. The method is flexible, allowing for the production of 1-pentanol, 4-pentenoic acids, 1-pentanoic acids, and 4-pentenols having up to four substitutions at the 2 and 3 positions and up to one substitution at the 4 position of the 5-carbon chain. The method can be carried out using only a single purification procedure to produce pure product in good yield. The method can further provide products having a low percentage of structural isomers.

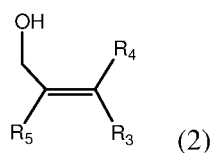
[0007] In brief, an ester of a carboxylic acid having two or more carbon atoms is transesterified with a 2-propenol to provide the corresponding 2-propenyl ester. In a preferred embodiment, one or both of the carboxylic acid ester and the 2-propenol are appropriately substituted. The 2-propenyl ester then undergoes rearrangement to produce a 4-propenoic acid. The 4-propenoic acid can be useful as an intermediate in other syntheses, or as itself in various applications. In an embodiment the 4-propenoic acid is used as a precursor that is reduced to provide a 1-pentanol, preferably a substituted 1-pentanol. Alternatively, the 4-propenoic acid is

used as a precursor that is reduced to provide a 4-pentenol, preferably a substituted 4-pentenol, or a 1-pentanoic acid, preferably a substituted 1-pentanoic acid.

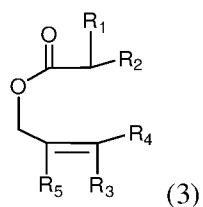
[0008] In particular, a carboxyl ester of formula (1)



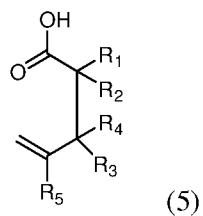
is transesterified with a 2-propenol of formula (2)



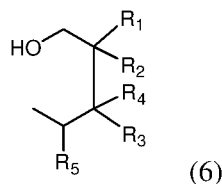
under conditions effective to provide 2-propenyl ester of formula (3),



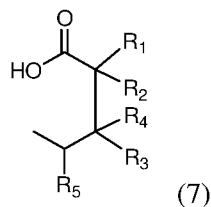
which is induced to undergo rearrangement to produce a 4-pentenoic acid of formula (5).



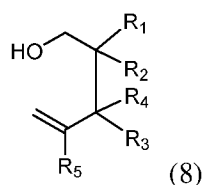
The 4-pentenoic acid of formula (5) can be reduced to provide the 1-pentanol of formula (6).



Alternatively, the 4-pentenoic acid of formula (5) can be reduced to provide the 1-pentanoic acid of formula (7).



Alternatively, the 4-pentenoic acid of formula (5) can be reduced to provide the the 4-pentenol of formula (8).



[0009] In the foregoing formulas (1), (2), (3), (4), (5), (6), (7), and (8), R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl, preferably methyl or ethyl; and each R₁, R₂, R₃, R₄, and R₅ is the same or different, and is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ arylalkylene. Preferably at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. Preferably two or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. In an embodiment, R₁ and R₅ are not hydrogen. Further, each R₁, R₂, R₃, R₄, and R₅ is independently unsubstituted or substituted with 1 to 6, preferably 1 to 3 substituents, wherein each substituent is independently cyano, nitro, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, benzyl, phenyl, or phenyl optionally substituted with 1 to 4 groups that can be the same or different, and which groups are cyano, nitro, halogen, C₁₋₆ alkyl, benzyl, or phenyl.

[0010] In some embodiments in the foregoing formulas (1), (2), (3), (4), (5), (6), (7), and (8), R is a C₁₋₃ alkyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₁₂ alkyl, C₇₋₂₂ alkenyl, C₁₋₁₁ heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₇ heterocycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or C₇₋₁₁ arylalkylene. Preferably at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. Preferably two or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. In an embodiment, R₁ and R₅ is not hydrogen. Further, each R₁, R₂, R₃, R₄, and R₅ is independently unsubstituted or substituted with 1 to 6, preferably 1 to 3 substituents, wherein each substituent is independently

cyano, nitro, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, benzyl, phenyl, or phenyl optionally substituted with 1 to 4 groups that can be the same or different, and which groups are cyano, nitro, halogen, C₁₋₆ alkyl, benzyl, or phenyl.

[0011] In other embodiments in the foregoing formulas (1), (2), (3), (4), (5), (6), (7), and (8), R is a C₁₋₃ alkyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₆ alkyl, C₇₋₁₈ alkenyl, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or benzyl. Preferably at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. Preferably two or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. In an embodiment, R₁ and R₅ are not hydrogen. Further, each R₁, R₂, R₃, R₄, and R₅ is independently unsubstituted or substituted with 1 to 6, preferably 1 to 3 substituents, wherein each substituent is independently cyano, nitro, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, benzyl, phenyl, or phenyl optionally substituted with 1 to 4 groups that can be the same or different, and which groups are cyano, nitro, halogen, C₁₋₆ alkyl, benzyl, or phenyl. Preferably, each R₁, R₂, R₃, R₄, and R₅ is unsubstituted.

[0012] In still other embodiments, in the foregoing formulas (1), (2), (3), (4), (5), (6), (7), and (8), R is methyl or ethyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen or C₁₋₃ alkyl. Preferably at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. Preferably two or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen. In an embodiment, R₁ and R₅ are not hydrogen. Further, each R₁, R₂, R₃, R₄, and R₅ is independently unsubstituted or substituted with 1 to 3 substituents, wherein each substituent is independently cyano, nitro, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, benzyl, phenyl, or phenyl optionally substituted with 1 to 4 groups that can be the same or different, and which groups are cyano, nitro, halogen, C₁₋₆ alkyl, benzyl, or phenyl. Preferably, each R₁, R₂, R₃, R₄, and R₅ is unsubstituted.

[0013] It is to be understood that the terms “2-propenol ” with reference to formula (2), “2-propenyl ester” with reference to formula (3), “4-pentenoic acid” with reference to formula (5), “1-pentanol” with reference to formula (6), “1-pentanoic acid” with reference to formula (7), and “4-pentenol” with reference to formula (8) are terms of convenience that refer to the essential 5-carbon backbone of each compound, rather than to the formal name of each compound. Thus, a compound of formula (5) wherein R₁, R₂, R₃, and R₅ is hydrogen and R₄ is octyl can nonetheless be referred to herein as a 4-pentenoic acid of formula (5) for convenience.

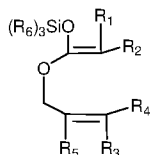
[0014] Transesterifying the carboxyl ester of formula (1) with the 2-propenol of formula (2) can be effected under known transesterification conditions, for example by heating, optionally in the presence of a solvent, and optionally in the presence of a transesterification catalyst. Solvents that can be used can be any inert solvent such as cyclohexane, 2-methylhexane, 3-methylhexane, hexane, toluene, benzene, xylene, or methylene chloride.

Transesterification can be carried out without solvent, in which case the reactants are combined together. The product alcohol (ROH) can be removed, for example as an azeotrope during transesterification.

[0015] A transesterification catalyst, such as a metal, acid, or base catalyst can be used. Metal catalysts can include antimony, manganese, cobalt, zirconium, zinc, aluminum, or titanium, for example organic titanates such as tetraisopropyl and tetra n-butyl titanates. Acid catalysts can be inorganic or organic, such as methanesulfonic acid or toluene sulfonic acid. Basic catalysts can be non-ionic bases, such as amines, amidines, guanidines, and triamino(imino)phosphoranes. The base catalyst can be inorganic, such as metal carbonates, hydroxides, oxides, or alkoxides, for example alkali or alkaline earth hydroxides, carbonates, oxides or methoxides, more preferably hydroxide, oxide or carbonate salts of sodium, potassium, barium, calcium or magnesium, or a carbonate or hydroxide salt of sodium, potassium or calcium.

[0016] The concentration of catalyst used in the transesterification can be 0.01 to 10 weight percent (wt%), or 0.1 to 2 wt%, based on the total weight of the carboxyl ester (1) or the total weight of the reactants. Transesterification can be carried out at temperatures above room temperature, such as 22 or 25°C to 200°C, preferably from 40°C to 100°C, under a pressure of 1 to 500 atmospheres or higher, or 0.001 to 1 atmosphere, for a time period of 0.2 to 20 hours, or 0.3 to 15 hours, or 0.5 to 10 hours. The carboxyl ester of formula (1) and the 2-propenol of formula (2) can be present in equimolar amounts, or an excess of the 2-propenol of formula (2) can be used, for example a ratio of 2-propenol to carboxyl ester of 1:1 to 10:1, or 1:1 to 5:1, or 1:1 to 4:1.

[0017] The 2-propenyl ester of formula (3) is converted to the 4-pentenoic acid of formula (5) via a rearrangement, in particular using an Ireland-Claisen type rearrangement. Without being bound by theory, this reaction proceeds according to the Woodward-Hoffmann rules with a [3,3]-sigmatropic concerted, suprafacial, pericyclic mechanism and with a high degree of stereoselectivity. The rearrangement is initiated by contacting the 2-propenyl ester of formula (3) with an organic base such as lithium diisopropylamide or n-butyl lithium and a trialkylsilyl halide of formula $\text{XSi}(\text{R}_6)_3$ wherein each R_6 is independently a C_{1-8} alkyl or C_{6-10} aryl, specifically a C_{1-6} alkyl or phenyl, and X is a halogen, for example trimethylsilyl chloride, triethylsilyl chloride, tripropylsilyl chloride, tert-butyldimethylsilyl chloride, or tert-butyldiphenylsilyl chloride. Without being bound by theory, it is believed that the rearrangement proceeds via an enolization and silylation of the enol to provide the intermediate of formula (4)

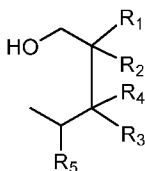


(4)

wherein R₁, R₂, R₃, R₄, and R₅ are as described above.

[0018] The rearrangement can proceed using the solvent from the transesterifying step (provided that the solvent is inert, e.g., hexane, toluene, benzene, xylene or methylene chloride), at low temperature. Alternatively the 2-propenyl ester of formula (3) can be isolated and a suitable solvent such as tetrahydrofuran (THF) or hexamethylphosphoramide (HMPT) can be added. Temperatures can be, for example, -20 to -100°C or -60 to -100°C. The organic base can be present in a concentration of 0.01 to 5 wt%, based on the total weight of the reaction mixture. Preferably the intermediate (4) is not isolated. Instead, rearrangement is allowed or induced, for example by raising the reaction temperature to -10 to 80°C, for example in stages such as -10 to 25°C, and then to 30 to 80°C, or from 10 to 23°C and then to 45 to 60°C, to produce the readily hydrolyzable silyl enol ester (4). Thus, the 4-pentenoic acid of formula (5) can be isolated from the reaction mixture by standard techniques such as addition of an aqueous phase and extraction.

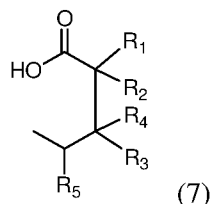
[0019] The 4-pentenoic acid of formula (5) can be reduced, i.e., hydrogenated, to provide various products. In some embodiments, the 4-pentenoic acid of formula (5) is reduced to provide the 1-pentanol of formula (6)



(6)

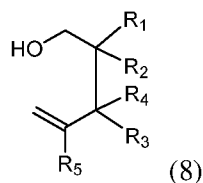
wherein R₁, R₂, R₃, R₄, and R₅ are as described above. Reduction conditions can include exposing the 4-pentenoic acid of formula (5) to hydrogen in the presence of a metal catalyst under pressure. Various catalysts can be used, preferably Raney-nickel. Reducing can be conducted at any suitable temperature that allows the reaction to occur, such as room temperature or higher, e.g., 22°C to 200°C, or 40°C to 100°C, and any suitable pressure, for example 1 to 500 atmospheres or higher. An inert solvent can be used, such as various dialkyl ethers, aliphatic alcohols, or dioxane. Isolation of the 1-pentanol of formula (6) can be by any method, for example filtering to remove the metal catalyst and removal of any solvent.

[0020] In other embodiments, the 4-pentenoic acid of formula (5) is reduced to provide the 1-pentanoic acid of formula (7)



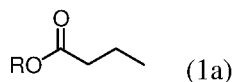
wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as described above. Reduction conditions can include exposing the 4-pentenoic acid of formula (5) to hydrogen in the presence of a metal catalyst under pressure. Various catalysts can be used, for example a selective palladium-containing catalyst. Reducing can be conducted at any suitable temperature that allows the reaction to occur, such as room temperature or higher, e.g., 22°C to 200°C, or 40°C to 100°C, and any suitable pressure, for example 1 to 500 atmospheres or higher. An inert solvent can be used, such as various dialkyl ethers, aliphatic alcohols, or dioxane. Isolation of the 1-pentanoic acid of formula (7) can be by any method, for example filtering to remove the metal catalyst and removal of any solvent.

[0021] In still other embodiments, the 4-pentenoic acid of formula (5) is reduced to provide the 4-pentenol of formula (8).

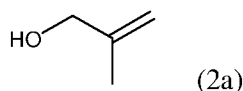


wherein R_1 , R_2 , R_3 , R_4 , and R_5 are as described above. Reduction conditions can include exposing the 4-pentenoic acid of formula (5) to a reducing agent such as LiAlH_4 . Reducing can be conducted at any suitable temperature that allows the reaction to occur. An inert solvent can be used, such as various dialkyl ethers, aliphatic alcohols, or dioxane. Isolation of the 4-pentenol of formula (8) can be by any method, for example filtering or extraction to remove the metal catalyst and removal of any solvent.

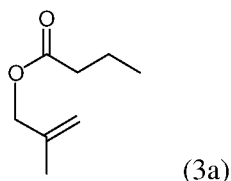
[0022] A specific embodiment of the foregoing methods is a synthesis of 2-ethyl-4-methyl-1-pentanol and its precursor 2-ethyl-4-methyl-4-pentenoic acid. The method includes transesterifying a butyrate ester of formula (1a)



wherein R is a C_{1-6} alkyl, preferably a C_{1-3} alkyl, more preferably methyl or ethyl, with 2-methyl-2-propenol of formula (2a)

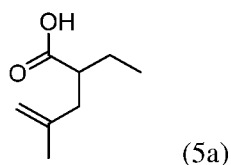


under conditions effective to provide 2-methyl-2-propenyl butyrate of formula (3a).

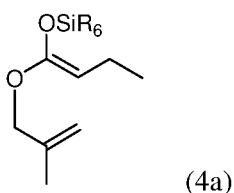


The transesterification conditions can be as described above. In an embodiment the transesterification catalyst is a tetraisopropyl titanate, and the reaction is conducted with concomitant removal of ROH.

[0023] The 2-methyl-2-propenyl butyrate (3a) is subjected to conditions effective to provide 2-ethyl-4-methyl-4-pentenoic acid of formula (5a)

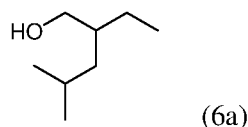


with high selectivity. Conditions for the rearrangement can include reacting the 2-methyl-2-propenyl butyrate with a base such as butyllithium or lithium diisopropylamide in the presence of a chlorosilane as described above, which without being bound by theory is believed to provide the silyl enolate intermediate of formula (4a)

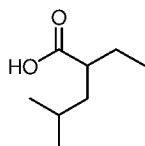


which upon acidification provides 2-ethyl-4-methyl-4-pentenoic acid (5a).

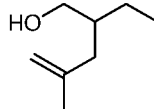
[0024] The 2-ethyl-4-methyl-4-pentenoic acid (5a) is reduced under conditions effective to provide 2-ethyl-4-methyl-1-pentanol of formula (6a).



Effective conditions include hydrogenation as described above, in particular hydrogenation using Raney nickel. In other embodiments, selective hydrogenation as described above is used to provide the 2-ethyl-4-methyl-1-pentanoic acid of formula (7a) or the 2-ethyl-4-methyl-4-penten-1-ol of formula (8a).



(7a)



(8a)

[0025] The 4-pentenoic acid of formula (5) can contain greater than 75 wt%, preferably greater than 80 wt%, preferably greater than 90 wt% of the desired structural isomer product, as compared to other structural isomers. Preferably the percentage of structural isomers of formula (5) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

[0026] In some embodiments, the 4-pentenoic acid of formula (5) or (5a) is used as itself in various applications, for example as a surfactant, or as a polymer or food additive (e.g., as a plasticizer or as an additive to an animal feed or human food). The specific application will depend on the structure of the 4-pentenoic acid of formula (5). For example, when R₃ or R₄ is a long-chain alkyl or alkenyl group, such as a C₇₋₂₂ alkyl or C₇₋₂₂ alkenyl, the compound can function as a surfactant or an equivalent of a long-chain fatty acid. Alternatively the 4-pentenoic acids of formula (5) can be esterified with an alcohol, amine, or reactive derivative thereof, and the ester or amide used as a plasticizer, surfactant, or additive, or as an intermediate in pharmaceutical or polymer synthesis.

[0027] The 1-pentanol of formula (6) can contain greater than 75 wt%, preferably greater than 80 wt%, preferably greater than 90 wt% of the desired structural isomer, as compared to other structural isomers. Preferably the percentage of undesired structural isomers of formula (6) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

[0028] The 1-pentanol of formula (6) are also useful in various applications, for example as a surfactant or as a polymer or food additive (e.g., as a plasticizer or an additive to an animal feed or human food). Alternatively the 1-pentanol of formula (6) can be esterified with a carboxylic acid or reactive derivative thereof, or reacted with an isocyanate, and the ester or urethane used as a plasticizer, surfactant, or additive, or as an intermediate in pharmaceutical or polymer synthesis. In addition, EMPOH is an impurity formed during the synthesis of 2-ethylhexanol (2-EH), which is itself used in the synthesis of plasticizers. The methods disclosed herein provide ready access to EMPOH that can be used as reference standard to determine the purity of 2-EH.

[0029] The 1-pentanoic acid of formula (7) can contain greater than 75 wt%, preferably greater than 80 wt%, preferably greater than 90 wt% of the desired structural isomer, as compared to other structural isomers. Preferably the percentage of undesired structural isomers

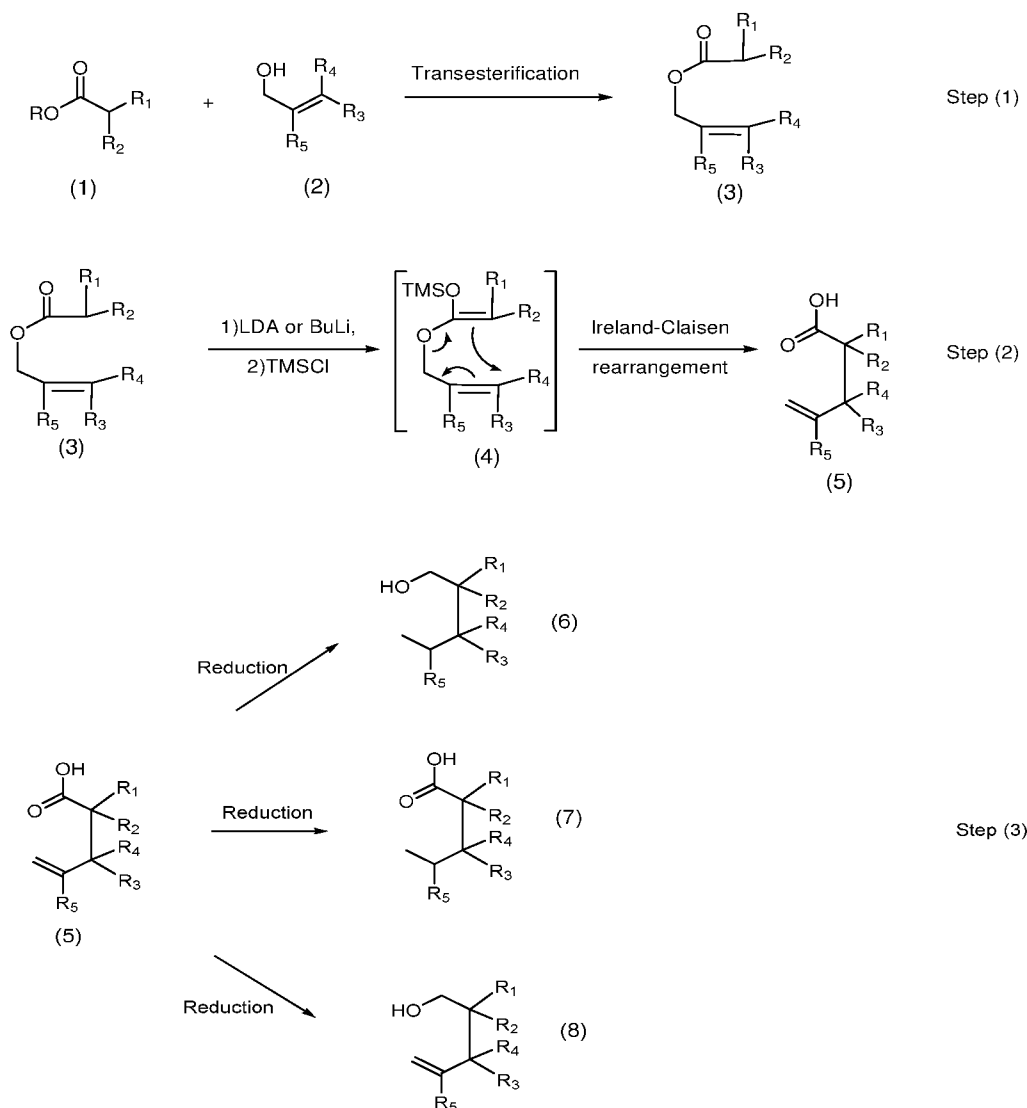
of formula (7) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%. The 1-pentanoic acids of formula (7) are also useful in various applications, for example as a surfactant or as a polymer or food additive (e.g., as a plasticizer or an additive to an animal feed or human food). Alternatively the 1-pentanoic acids of formula (7) can be esterified with an alcohol or reactive derivative thereof, or reacted with an isocyanate, and the ester or urethane used as a plasticizer, surfactant, or additive, or as an intermediate in pharmaceutical or polymer synthesis.

[0030] The 4-pentenol of formula (8) can contain greater than 75 wt%, preferably greater than 80 wt%, preferably greater than 90 wt% of the desired structural isomer, as compared to other structural isomers. Preferably the percentage of undesired structural isomers of formula (8) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%. The 4-pentenols of formula (8) are also useful in various applications, for example as a surfactant or as a polymer or food additive (e.g., as a plasticizer or an additive to an animal feed or human food). Alternatively 4-pentenols of formula (8) can be esterified with a carboxylic acid or reactive derivative thereof, or reacted with an isocyanate, and the ester or urethane used as a plasticizer, surfactant, or additive, or as an intermediate in pharmaceutical or polymer synthesis.

[0031] This disclosure is further illustrated by the following examples, which are non-limiting.

EXAMPLES

[0032] A method for the synthesis of a 1-pentanol of formula (6), including an optionally 2,2,3,4,4-pentasubstituted 1-pentanol is shown in Scheme 1. In Scheme 1, an ester of a carboxylic acid containing 2 or more carbon atoms is transesterified to provide the 2-propenyl ester. The ester can be optionally isolated or isolated and purified. The 2-propenyl ester is reacted with a base such as butyllithium (or lithium diisopropylamide, LDA) in the presence of trimethylchlorosilane (TMSCl) to provide the corresponding silyl enol ether intermediate. Without purifying the intermediate, the reaction system is heated and acidified to provide the 4-pentenoic acid. The pentenoic acid derivative is completely reduced, for example under Raney nickel and hydrogen to provide the 1-pentanol (6), or selectively reduced, for example in the presence of a palladium catalyst, to provide the 1-pentanoic acid (7) or the 4-pentenol (8).



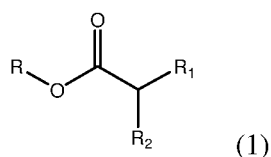
Scheme 1.

Example 1.

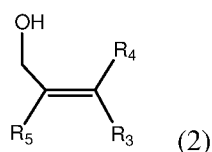
[0033] A specific embodiment of the foregoing methods is a synthesis of 2-ethyl-4-methyl-1-pentanol and its precursor 2-ethyl-4-methyl-4-pentenoic acid. Ethyl or methyl butyrate is transesterified with 2-methyl-2-propen-1-ol in the presence of a catalyst to provide 2-methyl-2-propenyl butyrate. The 2-methyl-2-propenyl butyrate is treated with *n*-butyllithium and TMSCl at a temperature below 0°C to provide the intermediate silyl enol ether, which is allowed to warm to room temperature and then heated if necessary to effect rearrangement. The product is acidified to provide 2-ethyl-4-methyl-4-pentenoic acid. The 2-ethyl-4-methyl-4-pentenoic acid (5a) is hydrogenated in the presence of Raney-nickel at room temperature to provide 2-ethyl-4-methyl-1-pentanol (6), or in the presence of a selective palladium catalyst to provide 2-ethyl-4-methyl-1-pentanol (7).

[0034] The methods, compositions, and other aspects are further illustrated by the Embodiments below.

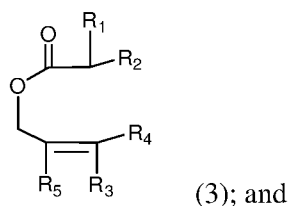
[0035] Embodiment 1: A synthetic method, comprising transesterifying a carboxyl ester of formula (1)



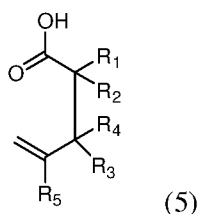
with a 2-propenol of formula (2)



under conditions effective to provide a 2-propenyl ester of formula (3)

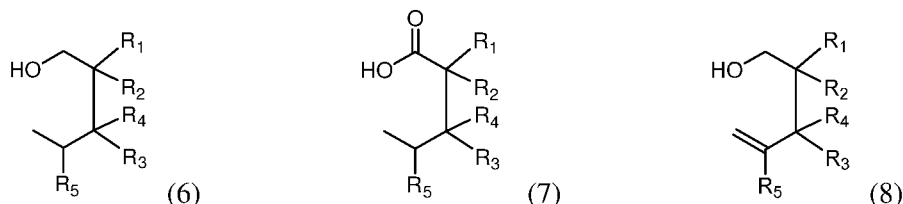


reacting the 2-propenyl ester of formula (3) under conditions effective to provide a 4-pentenoic acid of formula (5)



wherein in the foregoing formulas R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl; and each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ arylalkylene, preferably wherein at least one R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

[0036] Embodiment 2: The method of Embodiment 1, further comprising reducing the 4-pentenoic acid of formula (5) under conditions effective to provide a 1-pentanol of formula (6) or a 1-pentanoic acid of formula (7) or a 4-pentenol of formula (8).



[0037] Embodiment 3: The method of Embodiment 1 or 2, wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₁₂ alkyl, C₇₋₂₂ alkenyl, C₁₋₁₁ heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₇ heterocycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or C₇₋₁₁ arylalkylene, preferably wherein at least one R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

[0038] Embodiment 4: The method of any one or more of Embodiments 1 to 3, wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or benzyl, preferably wherein at least one or at least two R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

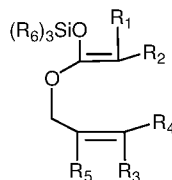
[0039] Embodiment 5: The method of any one or more of Embodiments 1 to 4, wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen or C₁₋₃ alkyl preferably wherein at least one or at least two R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

[0040] Embodiment 6: The method of any one or more of Embodiments 2 to 5, wherein the 1-pentanol of formula (6) is 2-ethyl-4-methyl-1-pentanol.

[0041] Embodiment 7: The method of any one or more of Embodiments 1 to 6, wherein transesterifying is by heating, optionally in the presence of a solvent, and optionally in the present of a transesterification catalyst.

[0042] Embodiment 8: The method of any one or more of Embodiments 1 to 7, wherein reacting the 2-propenyl ester of formula (3) comprises reacting in the presence of an organic base, preferably lithium diisopropylamide or n-butyllithium and a trialkylsilyl halide of formula XSi(R₆)₃ wherein each R₆ is independently a C₁₋₈ alkyl or C₆₋₁₀ aryl, specifically a C₁₋₆ alkyl or phenyl, and X is a halogen; followed by heating.

[0043] Embodiment 9: The method of Embodiment 8, wherein reacting the 2-propenyl ester of formula (3) in the presence of the organic base and the trialkylsilyl halide provides an intermediate of formula (4)



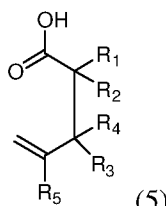
(4)

wherein each R_6 is independently a C_{1-8} alkyl or C_{6-10} aryl, specifically a C_{1-8} alkyl or phenyl, preferably methyl, ethyl, or isopropyl.

[0044] Embodiment 10: The method of Embodiment 9, wherein the intermediate (4) is not isolated.

[0045] Embodiment 11: The method of any one or more of Embodiments 2 to 10, wherein reducing is under hydrogen in the presence of a catalyst, preferably Raney-nickel, to provide the 1-pentanol of formula (6) or in the presence of a selective catalyst, preferably a palladium compound, to provide the 1-pentanoic acid of formula (7), or in the presence of lithium aluminum hydride to provide the 4-pentenol of formula (8).

[0046] Embodiment 12: A 4-pentenoic acid of formula (5), preferably made by the method of any one or more of Embodiments 1 or 3 to 10,

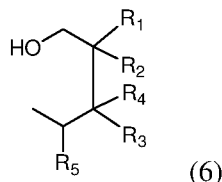


(5)

wherein each R_1 , R_2 , R_3 , R_4 , and R_5 is independently a hydrogen, C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{1-21} heteroalkyl, C_{3-12} cycloalkyl, C_{3-11} heterocycloalkyl, C_{6-12} aryl, C_{6-11} heteroaryl, or C_{7-13} alkylenearyl; preferably wherein one of R_3 and R_4 is a hydrogen, and the other is a C_{7-22} alkyl or C_{7-22} alkenyl; and preferably wherein the percentage of structural isomers of formula (5) made by the method is less than 10 wt %, or less than 5 wt %, or less than 1 wt %.

[0047] Embodiment 13: A composition comprising the 4-pentenoic acid of formula (5) of Embodiment 12.

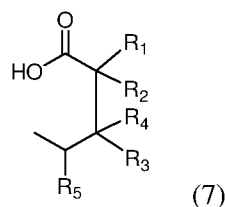
[0048] Embodiment 14: A 1-pentanol of formula (6), preferably made by the method of any one or more of Embodiments 2 to 11,



wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl.

[0049] Embodiment 15: A composition comprising the 1-pentanol of formula (6) of Embodiment 14.

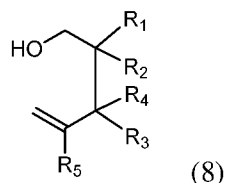
[0050] Embodiment 16: A 1-pentanoic acid of formula (7), preferably made by the method of any one or more of Embodiments 2 to 11,



wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl; preferably wherein one of R₃ and R₄ is a hydrogen, and the other is a C₇₋₂₂ alkyl; and preferably wherein the percentage of structural isomers of formula (7) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

[0051] Embodiment 17: A composition comprising the 1-pentanoic acid of formula (7) of Embodiment 16.

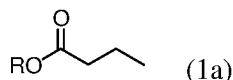
[0052] Embodiment 18: A 4-pentenol acid of formula (8), optionally made by the method of any one or more of Embodiments 1 or 3 to 10,



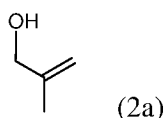
wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl; preferably wherein the percentage of structural isomers of formula (8) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

[0053] Embodiment 19: A composition comprising the 4-pentenol of formula (8) of Embodiment 18.

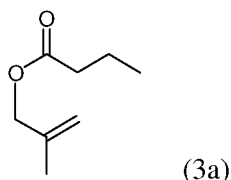
[0054] Embodiment 20: A method for the synthesis of 2-ethyl-4-methyl-1-pentanol, the method comprising transesterifying a butyrate ester of formula (1a)



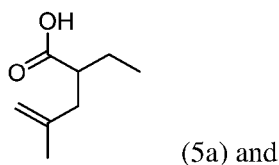
wherein R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl, with 2-methyl-2-propenol of formula (2a)



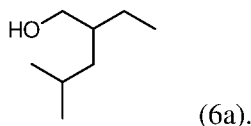
under conditions effective to provide 2-methyl-2-propenyl butyrate of formula (3a);



reacting the 2-methyl-2-propenyl butyrate of formula (3a) under conditions effective to provide 2-ethyl-4-methyl-4-pentenoic acid of formula (5a);



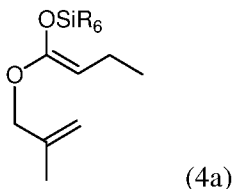
reducing the 2-ethyl-4-methyl-4-pentenoic acid of formula (5a) under conditions effective to provide 2-ethyl-4-methyl-1-pentanol of formula (6a)



[0055] Embodiment 21: The method of Embodiment 20, wherein transesterifying is by heating, optionally in the presence of a solvent, and optionally in the presence of a transesterification catalyst.

[0056] Embodiment 22: The method of Embodiment 20 or 21, wherein reacting the 2-methyl-2-propenyl butyrate of formula (3a) is in the presence of lithium diisopropylamide or n-butyl lithium and a trialkylsilyl halide of formula XSi(R₆)₃ wherein each R₆ is independently a C₁₋₃ alkyl and X is a halogen; preferably followed by heating.

[0057] Embodiment 23: The method of Embodiment 22, wherein reacting the 2-methyl-2-propenyl butyrate of formula (3a) provides an intermediate of formula (4a)



which rearranges to provide 2-ethyl-4-methyl-4-pentenoic acid of formula (5a) during heating.

[0058] Embodiment 24: The method of Embodiment 22 or Embodiment 23, wherein the intermediate of formula (4a) is not isolated.

[0059] Embodiment 25: The method of any one or more of Embodiments 20 to 24, wherein reducing is under hydrogen in the presence of a catalyst, preferably Raney-nickel.

[0060] Embodiment 26: 2-Ethyl-4-methyl-1-pentanol made by the method any one or more of Embodiments 20 to 25.

[0061] Embodiment 27: A composition comprising the 2-ethyl-4-methyl-1-pentanol of formula (6a) of Embodiment 26.

[0062] In general, the methods and compositions can alternatively comprise, consist of, or consist essentially of, any appropriate steps or components herein disclosed. The methods and compositions can additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any steps, components, materials, ingredients, adjuvants or species that are otherwise not necessary to the achievement of the function and/or objectives of the present claims.

[0063] All ranges disclosed herein are inclusive of the endpoints, and the endpoints are independently combinable with each other. The terms “a” and “an” and “the” herein do not denote a limitation of quantity, and are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. “Or” means “and/or” unless clearly stated otherwise. “Combination” is inclusive of blends, mixtures, alloys, reaction products, and the like. Furthermore, the terms “first,” “second,” and the like, herein do not denote any order, quantity, or importance, but rather are used to denote one element from another. It is to be understood that the described elements may be combined in any suitable manner in the various embodiments.

[0064] The following definitions are used herein. The term “alkyl” includes branched or straight chain, unsaturated aliphatic hydrocarbon groups e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n- and s-hexyl, n- and s-heptyl, and, n- and s-octyl. “Cycloalkyl” refers to a non-aromatic monovalent monocyclic or multicyclic hydrocarbon group having at least three carbon atoms. “Aryl” refers to an aromatic monovalent group containing

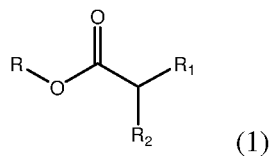
only carbon in the aromatic ring or rings. "Alkenyl" means a straight or branched chain, monovalent hydrocarbon group having at least one carbon-carbon double bond (e.g., ethenyl (-HC=CH₂)). "Alkoxy" means an alkyl group that is linked via an oxygen (i.e., alkyl-O-), for example methoxy, ethoxy, and sec-butyloxy groups. "Alkylene" means a straight or branched chain, saturated, divalent aliphatic hydrocarbon group (e.g., methylene (-CH₂-) or propylene (-CH₂)₃-). "Cycloalkylene" means a divalent cyclic alkylene group, -C_nH_{2n-x}, wherein x is the number of hydrogens replaced by cyclizations. "Arylalkylene" refers to an alkyl group that has been substituted with an aryl group as defined above, with benzyl being an exemplary arylalkylene group. "Halogen" or the prefix "halo" means a group or compound including one more of a fluoro, chloro, bromo, iodo, and astatino substituent. A combination of different halo groups (e.g., bromo and fluoro) can be present. In an embodiment only chloro groups are present. The prefix "hetero" means that the compound or group includes at least one heteroatom (e.g., 1, 2, or 3 heteroatom(s)), wherein the heteroatom(s) is each independently N, O, S, or P, and wherein the heteroatom(s) can be a ring member.

[0001] Unless otherwise indicated, each of the foregoing groups can be unsubstituted or substituted, provided that the substitution does not significantly adversely affect synthesis, stability, or use of the compound. "Substituted" means that the compound or group is substituted with at least one (e.g., 1, 2, 3, 4, 5, or 6) substituents, preferably 1 to 3 substituents, which substituents are independently a cyano (-CN), a nitro (-NO₂), a halogen, a C₁₋₆ alkyl, a C₁₋₆ alkoxy, a C₃₋₆ cycloalkyl, benzyl, phenyl, or phenyl optionally substituted with 1 to 4 groups that can be the same or different, and which groups are cyano, nitro, halogen, C₁₋₆ alkyl, benzyl, or phenyl, instead of hydrogen, provided that the substituted atom's normal valence is not exceeded. As used herein, the term "hydrocarbyl" and "hydrocarbon" refers broadly to a substituent comprising carbon and hydrogen, optionally with 1 to 3 heteroatoms, for example, oxygen, nitrogen, halogen, silicon, sulfur, or a combination thereof. Combinations of substituents and/or variables are permissible provided that the substitutions do not significantly adversely affect synthesis or use of the compound. "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event occurs and instances where it does not.

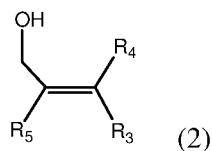
[0065] While particular embodiments have been described, alternatives, modifications, variations, improvements, and substantial equivalents that are or may be presently unforeseen may arise to applicants or others skilled in the art. Accordingly, the appended claims as filed and as they may be amended are intended to embrace all such alternatives, modifications, variations, improvements, and substantial equivalents.

CLAIMS

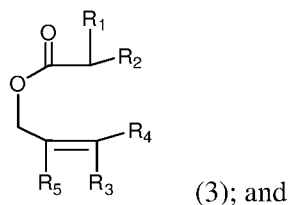
1. A synthetic method, comprising:
transesterifying a carboxyl ester of formula (1)



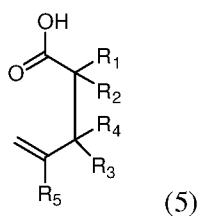
with a 2-propenol of formula (2)



under conditions effective to provide a 2-propenyl ester of formula (3)



reacting the 2-propenyl ester of formula (3) under conditions effective to provide a 4-pentenoic acid of formula (5)

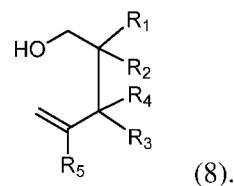
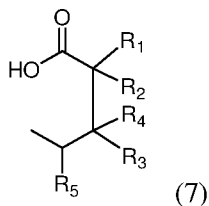
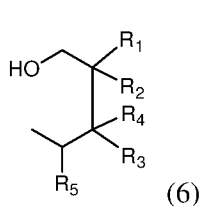


wherein in the foregoing formulas

R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl; and

each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ arylalkylene, preferably wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

2. The method of claim 1, further comprising reducing the 4-pentenoic acid of formula (5) under conditions effective to provide a 1-pentanol of formula (6) or a 1-pentanoic acid of formula (7) or a 4-pentenol of formula (8)



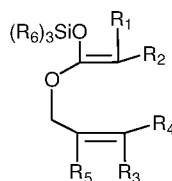
3. The method of claim 1 or 2, wherein
 each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₁₂ alkyl, C₇₋₂₂ alkenyl, C₁₋₁₁ heteroalkyl, C₃₋₈ cycloalkyl, C₃₋₇ heterocycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or C₇₋₁₁ arylalkylene, preferably wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; or
 wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl, C₆₋₉ heteroaryl, or benzyl, preferably wherein at least one or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen; or
 wherein each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen or C₁₋₃ alkyl, preferably wherein at least one of R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

4. The method of any one or more of claims 2 to 5, wherein the 1-pentanol of formula (6) is 2-ethyl-4-methyl-1-pentanol.

5. The method of any one or more of claims 1 to 4, wherein transesterifying is by heating, optionally in the presence of a solvent, and optionally in the presence of a transesterification catalyst.

6. The method of any one or more of claims 1 to 5, wherein reacting the 2-propenyl ester of formula (3) comprises reacting in the presence of an organic base, preferably lithium diisopropylamide or n-butyllithium and a trialkylsilyl halide of formula XSi(R₆)₃ wherein each R₆ is independently a C₁₋₈ alkyl or C₆₋₁₀ aryl, specifically a C₁₋₆ alkyl or phenyl, and X is a halogen; followed by heating.

7. The method of claim 6, wherein reacting the 2-propenyl ester of formula (3) in the presence of the organic base and the trialkylsilyl halide provides an intermediate of formula (4)



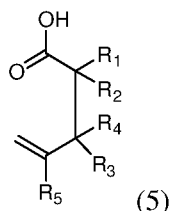
(4)

wherein each R_6 is independently a C_{1-8} alkyl or C_{6-10} aryl, specifically a C_{1-8} alkyl or phenyl, preferably methyl, ethyl, or isopropyl.

8. The method of claim 7, wherein the intermediate (4) is not isolated.

9. The method of any one or more of claims 2 to 8, wherein reducing is under hydrogen in the presence of a catalyst, preferably Raney-nickel, to provide the 1-pentanol of formula (6) or in the presence of a selective catalyst, preferably a palladium compound, to provide the 1-pentanoic acid of formula (7), or in the presence of lithium aluminum hydride to provide the 4-pentenol of formula (8).

10. A 4-pentenoic acid of formula (5), optionally made by the method of any one or more of claims 1 or 3 to 9,



(5)

wherein

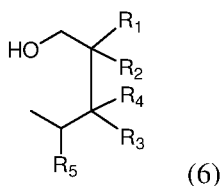
each R_1 , R_2 , R_3 , R_4 , and R_5 is independently a hydrogen, C_{1-22} alkyl, C_{1-22} alkoxy, C_{2-22} alkenyl, C_{1-21} heteroalkyl, C_{3-12} cycloalkyl, C_{3-11} heterocycloalkyl, C_{6-12} aryl, C_{6-11} heteroaryl, or C_{7-13} alkylenearyl;

preferably wherein one of R_3 and R_4 is a hydrogen, and the other is a C_{7-22} alkyl or C_{7-22} alkenyl; and

preferably wherein the percentage of structural isomers of formula (5) made by the method is less than 10 wt %, or less than 5 wt %, or less than 1 wt %.

11. A composition comprising the 4-pentenoic acid of formula (5) of claim 10.

12. A 1-pentanol of formula (6), optionally made by the method of any one or more of claims 2 to 9,

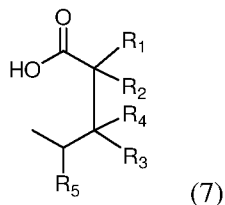


wherein

each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl, preferably wherein at least one or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen.

13. A composition comprising the 1-pentanol of formula (6) of claim 12.

14. A 1-pentanoic acid of formula (7), optionally made by the method of any one or more of claims 2 to 9,



wherein

each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl;

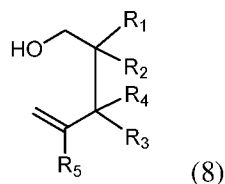
preferably wherein at least one or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen;

preferably wherein one of R₃ and R₄ is a hydrogen, and the other is a C₇₋₂₂ alkyl; and

preferably wherein the percentage of structural isomers of formula (5) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

15. A composition comprising the 1-pentanoic acid of formula (7) of claim 14.

16. A 4-pentenol of formula (8), optionally made by the method of any one or more of claims 1 or 2 to 9,



wherein

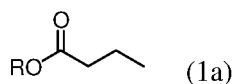
each R₁, R₂, R₃, R₄, and R₅ is independently a hydrogen, C₁₋₂₂ alkyl, C₁₋₂₂ alkoxy, C₂₋₂₂ alkenyl, C₁₋₂₁ heteroalkyl, C₃₋₁₂ cycloalkyl, C₃₋₁₁ heterocycloalkyl, C₆₋₁₂ aryl, C₆₋₁₁ heteroaryl, or C₇₋₁₃ alkylenearyl, preferably wherein at least one or at least two of R₁, R₂, R₃, R₄, and R₅ is not hydrogen;

preferably wherein the percentage of structural isomers of formula (8) made by the method is less than 10 wt %, or less than 5 wt%, or less than 1 wt%.

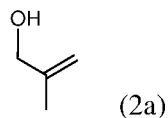
17. A composition comprising the 4-pentenol of formula (8) of claim 16.

18. A method for the synthesis of 2-ethyl-4-methyl-1-pentanol, the method comprising

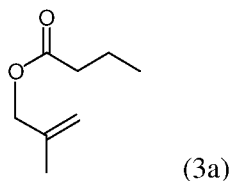
heating, optionally in the presence of a solvent, and optionally in the present of a transesterification catalyst, a butyrate ester of formula (1a)



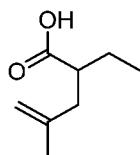
wherein R is a C₁₋₆ alkyl, preferably a C₁₋₃ alkyl, with 2-methyl-2-propenol of formula (2a)



under conditions effective to provide 2-methyl-2-propenyl butyrate of formula (3a);

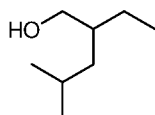


reacting, in the presence of lithium diisopropylamide or n-butyl lithium and a trialkylsilyl halide of formula XSi(R₆)₃ wherein each R₆ is independently a C₁₋₃ alkyl and X is a halogen, the 2-methyl-2-propenyl butyrate of formula (3a) under conditions effective to provide 2-ethyl-4-methyl-4-pentenoic acid of formula (5a), preferably followed by heating;



(5a) and

reducing, under hydrogen in the presence of a catalyst, preferably Raney-nickel, the 2-ethyl-4-methyl-4-pentenoic acid of formula (5a) under conditions effective to provide 2-ethyl-4-methyl-1-pentanol of formula (6a)



(6a).

19. 2-Ethyl-4-methyl-1-pentanol made by the method of claim 18.
20. A composition comprising the 2-ethyl-4-methyl-1-pentanol of formula (6a) of claim 19.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/057984

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C29/17 C07C67/03 C07C51/09
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DE 927 626 C (BASF AG) 12 May 1955 (1955-05-12) Example	12,13, 19,20
X	YOSHIRO OGATA ET AL: ".alpha.-Chlorination of aliphatic acids by molecular chlorine", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 40, no. 20, 1 October 1975 (1975-10-01), pages 2960-2962, XP055346456, ISSN: 0022-3263, DOI: 10.1021/jo00908a025 table III	14,15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

3 April 2017

Date of mailing of the international search report

20/04/2017

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/057984

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	DAUB G W ET AL: "Acyclic stereoselection in the ortho ester Claisen rearrangement", THE JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY ETC., vol. 62, no. 7, 4 April 1997 (1997-04-04), pages 1976-1985, XP002175162, ISSN: 0022-3263, DOI: 10.1021/J09614250	1,6-8
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X	NAAMA HEN ET AL: "Syntheses and Evaluation of Anticonvulsant Activity of Novel Branched Alkyl Carbamates", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 6, 22 March 2012 (2012-03-22) , pages 2835-2845, XP055346246, US	12,13
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/057984

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