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A stereoselective synthesis for the (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid and its monounsaturated analog (*Z*)-14-methyl-9-pentadecenoic acid

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Abstract—A stereoselective synthesis for the (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid and the monounsaturated analog (*Z*)-14-methyl-9-pentadecenoic acid was accomplished in six to seven steps where double alkyne coupling was the key step. This synthesis will facilitate the study of the topoisomerase I inhibitory profile of this important class of fatty acids.
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The (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid (**1**) is a bioactive fatty acid that was identified for the first time in the Caribbean gorgonian *Eunicea succinea*.[1] Such an acid was of interest because it is antimicrobial against *Staphylococcus aureus* (MIC 0.24 μmol/mL) and *Streptococcus faecalis* (MIC 0.16 μmol/mL).[1] In addition, acid **1** displays cytotoxicity against the epidermoid carcinoma (A431) cell line ($IC_{50} = 48$ μg/mL) and the lung carcinoma (NCI-H460) cell line ($IC_{50} = 51$ μg/mL).[2] Inhibition of human topoisomerase I is a possible mechanism of bioactivity for **1**. However, before the topoisomerase I inhibitory activity of **1** can be fully elucidated, a 100% stereoselective synthesis for **1** is still warranted since topoisomerase I inhibition is very sensitive to the double bond stereochemistry of fatty acids.[3] A previous six-step synthesis for acid **1** started with pent-4-yn-1-ol and combined alkyne-bromide coupling and Wittig reaction as a coupling combination to assemble the $\Delta^{5,9}$ functionality.[2] Unfortunately, this methodology afforded 95% of the desired (5*Z*,9*Z*) stereoisomer, but still 5% of the undesired (5*E*,9*Z*) stereoisomer was also obtained, which can affect the outcome of the topoisomerase I biological testing.[3] With this in mind we have developed herein a new synthetic route for this type of *iso*-branched fatty acids based on a double alkyne-bromide coupling reaction utilizing 1,5-hexadiyne (**3**) as the key starting material.

In addition, we have also accomplished the first total synthesis of the (*Z*)-14-methyl-9-pentadecenoic acid (**2**), a fatty acid that was first identified in several marine bacterial isolates, but it has never been synthesized.[4] Acid **2** has also the potential of displaying good topoisomerase I inhibitory activity since *iso*- and *anteiso* C_{15}–C_{17} fatty acids, isolated from a *Streptomyces* sp., displayed significant inhibition of topoisomerase I activity.[5]

Our synthesis for the (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid (**1**) started with commercially available 1,5-hexadiyne (**3**), which was monoalkylated with 1-bromo-4-methylpentane using *n*-BuLi in THF–HMPA affording, in a 48% yield, the monoalkylated adduct **4** (Scheme 1). The remaining open alkyne in the dialkyne was subsequently alkylated under identical reaction conditions with (4-bromobutoxy)-*tert*-butyldimethylsilane as the alkylating agent, which afforded the desired silylated pentadecadiyne **5** in a 44% yield. Deprotection of the *tert*-butyldimethylsilyl group was efficiently undertaken with tetrabutylammonium fluoride (TBAF) in THF affording alcohol **6** in an 81% isolated yield. The strategy of transforming first the alcohol to the aldehyde instead of going directly to the acid was followed for this synthesis, inasmuch as the alcohol was first converted into the aldehyde by reacting the 14-methyl-5,9-pentadecadiyn-1-ol with PCC in CH_2Cl_2 affording 14-methyl-5,9-pentadecadiynal in a 50% yield. Subsequent oxidation of the 14-methyl-5,9-pentadecadiynal with sodium chlorate ($NaClO_2$) and NaH_2PO_4 buffer in *tert*-butanol afforded the pentadecadiynoic acid **7** in a 34% isolated

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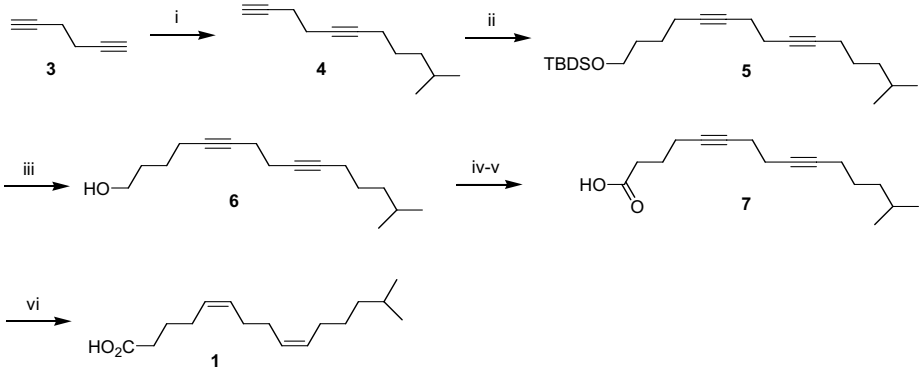

Scheme 1. Reagents and conditions: (i) *n*-BuLi, 1-bromo-4-methylpentane, THF–HMPA; (ii) *n*-BuLi, (4-bromobutoxy)-*tert*-butyl-dimethylsilane, THF–HMPA, −78 °C; (iii) TBAF, THF, rt; (iv) PCC, CH_2Cl_2, rt; (v) $NaClO_2$, *t*-BuOH, 48 h, rt; (vi) H_2, Lindlar.

yield. For the final step, catalytic hydrogenation of the dialkyne with 5% Pd/C in quinoline afforded the desired (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid (**1**) in a 52% yield and in 100% *Z*,*Z* stereoselectivity.[6] The overall yield for this six-step synthesis was 2% (Scheme 1).

The synthesis of (*Z*)-14-methyl-9-pentadecenoic acid (**2**) started with commercially available 4-methyl-1-bromopentane (**8**), which was transformed with *n*-butyllithium and trimethylsilylacetylene into the heptyne **9** in a 94% isolated yield (Scheme 2), which was further treated with sodium hydroxide in methanol yielding the expected 6-methyl-1-heptyne (**10**) in a 62% yield. Formation of the lithium acetylide of **10** with *n*-butyllithium in THF–HMPA, and subsequent addition of 8-(bromooctyloxy)-*tert*-butyldimethylsilane resulted in the isolation of the silylated pentadecyne **11** in a 33% yield. It is important to emphasize that in the lithium acetylide coupling reaction the bromoalkane must be added in HMPA, otherwise the cross coupling does not work as well. Reaction of **11** with tetrabutylammonium fluoride (TBAF) in THF afforded 14-methyl-9-pentadecyn-1-ol, which was isolated in a 79% yield. The 14-methyl-9-pentadecyn-1-ol was oxidized with pyridinium chlorochromate (PCC) in CH_2Cl_2 affording aldehyde **12** in a 99% yield. Further oxidation of the aldehyde with sodium chlorate ($NaClO_2$) and NaH_2PO_4 buffer in *tert*-butanol afforded the pentadecynoic acid **13** in a 52% yield. To finish the synthesis catalytic hydrogenation of the alkyne with 5% Pd/C in quinoline afforded the desired 14-methyl-9(*Z*)-pentadecenoic acid (**2**) in a 57% yield and in 100% *Z* stereoselectivity.[7] The overall yield for this seven-step synthesis was 4% (Scheme 2).

In summary, we have accomplished a stereoselective syntheses for the (5*Z*,9*Z*)-14-methyl-5,9-pentadecadienoic acid (**1**) and the monounsaturated analog (*Z*)-14-methyl-9-pentadecenoic acid (**2**), both novel candidates for topoisomerase I inhibition. Our synthetic approach is open to the synthesis of other similar but longer $\Delta^{5,9}$ fatty acids, such as the (5*Z*,9*Z*)-25-methyl-5,9-hexacosadienoic acid, which also inhibit topoisomerase I at lower concentrations and should provide access to these analogues for further biological evaluation.[8]

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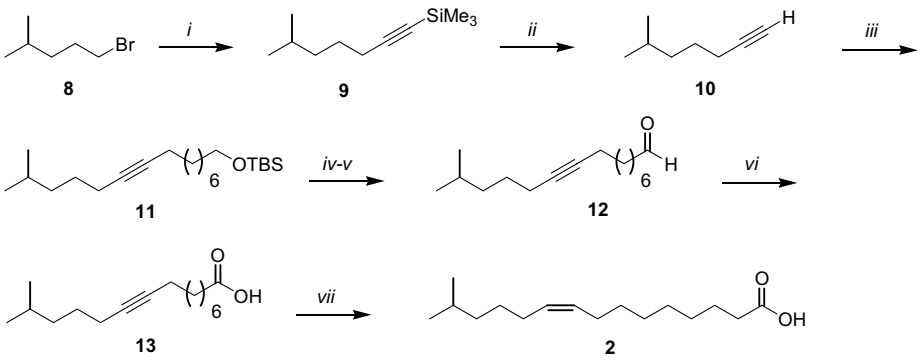

Scheme 2. Reagents and conditions: (i) trimethylsilylacetylene, *n*-BuLi, HMPA, THF, −78 °C; (ii) NaOH, MeOH, rt, 24 h; (iii) Br–$(CH_2)_8$–OTBS, *n*-BuLi, HMPA, THF, 0 °C, 48 h; (iv) TBAF, THF, 0 °C, 24 h; (v) PCC, CH_2Cl_2, rt, 24 h; (vi) $NaClO_2$, NaH_2PO_4-buffer, *t*-BuOH, 48 h; (vii) H_2, Pd/C, quinoline.

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7. Spectral data for acid **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.35 (m, 2H), 2.25 (t, $J = 7.51$ Hz, 2H), 2.15 (m, 4H), 2.00 (m, 1H), 1.65 (m, 2H), 1.33 (m, 4H), 1.25 (m, 8H), 0.87 (d, $J = 6.56$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7, 130.07, 130.03, 38.6, 34.6, 34.5, 33.8, 29.69, 29.67, 29.05, 29.03, 28.95, 27.6, 24.7, 22.7; GC–MS (70 eV) m/z (rel intensity): 254 (M^+, 10), 236 (5), 193 (3), 181 (9), 173 (2), 163 (7), 162 (2), 151 (4), 137 (6), 133 (3), 125 (6), 123 (9), 111 (15), 109 (10), 97 (28), 84 (27), 83 (40), 81 (25), 69 (99), 67 (32), 57 (53), 55 (100).
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