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A new stereoselective synthesis of biologically active di- and trienoic acids containing a (1*Z*,5*Z*)-diene moiety

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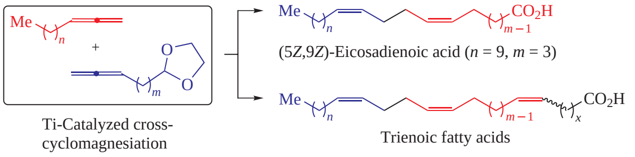
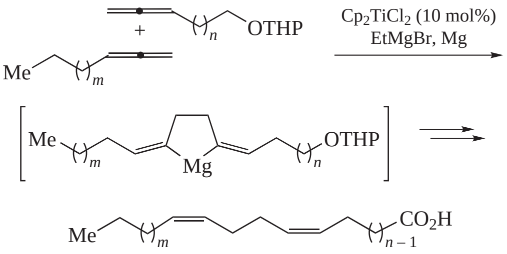
Natural (5*Z*,9*Z*)-dienoic acids and key precursors of biologically active trienoic acids were prepared in high yields and with high stereoselectivity using cross-cyclomagnesiation of terminal and oxygenated 1,2-dienes with EtMgBr in the presence of Mg metal and Cp_2TiCl_2 catalyst at the key step.



Unsaturated carboxylic acids, both natural and synthetic,[1–10] attract attention owing to their broad spectrum of biological properties. Di-, tri-, and polyenoic acids containing a (1*Z*,5*Z*)-diene moiety in the molecule, which are isolated in micro quantities from sea sponges and gymnosperm seeds, exhibit antiviral, antimicrobial, antitumor, antimalarial, and antituberculosis activities, and are also used as biologically active additives to reduce appetite in the treatment of obesity.[1,10–15]

Previously,[15–19] we performed a stereoselective synthesis of valuable higher (5*Z*,9*Z*)-dienoic acids in good yields (61–75%) and with high stereoselectivity (> 98%) in two steps using cross-cyclomagnesiation of tetrahydropyran ethers of terminal allenic alcohols with aliphatic 1,2-dienes (Scheme 1).



Scheme 1

As a development of these studies, herein we accomplished an alternative synthesis of (5*Z*,9*Z*)-eicosadienoic acid, which showed the highest inhibitory activity towards topoisomerase I.[15] We also demonstrated that this method is advantageous to prepare key building blocks for the synthesis of tri- and polyenoic acids containing a (1*Z*,5*Z*)-diene moiety, which are otherwise difficult to obtain.[10–14] The key idea in the development of the new method was to perform cross-cyclomagnesiation of aliphatic terminal allenes and ω-allenals on treatment with EtMgBr in the presence of a catalytic amount of Cp_2TiCl_2. We expected that this would give the aldehyde containing a (1*Z*,5*Z*)-diene group in one preparative step. Since aldehydes are not inert towards Grignard reagents, the retrosynthetic analysis included the use of ω-allenals with dioxolane protection.

The synthesis of (5*Z*,9*Z*)-eicosadienoic acid **5** was initiated by cross-cyclomagnesiation of 1,2-tridecadiene **1** and 2-(hexa-4,5-dien-1-yl)-1,3-dioxolane **2** (Scheme 2) with EtMgBr in the presence of Mg metal (halide ion acceptor) and Cp_2TiCl_2 catalyst (10 mol%) (**1** : **2** : EtMgBr : Mg : [Ti] ratio of 12 : 10 : 30 : 20 : 0.1, Et_2O, 20–22 °C, 7 h).† The reaction proceeded *via* the intermediate formation of magnesacyclopentane **3**, which was converted into linear (1*Z*,5*Z*)-diene **4** in 89% yield on treatment with a saturated aqueous solution of NH_4Cl. The subsequent oxidation of dioxolane **4** according to a known procedure[20] resulted in target (5*Z*,9*Z*)-eicosadienoic acid **5** in an overall yield of ~71%, synthesized previously in ~60% yield.[15]

The observed high chemoselectivity of formation of only the unsymmetrical magnesacyclopentane **3** is due to the fact that the reaction is carried out in diethyl ether in which, as was shown earlier,[21] the intermolecular catalytic cyclomagnesiation of aliphatic terminal allenes does not occur. The introduction of a slight excess of aliphatic 1,2-diene **1** completely suppresses the homo-cyclomagnesiation, and, hence, the formation of symmetrical magnesacyclopentanes; under the reaction conditions, they are produced in ~2% yield.

To develop a general protocol for the synthesis of trienoic acids containing a (1*Z*,5*Z*)-diene group, we carried out Ti-catalyzed cross-cyclomagnesiation of 1,2-dienes **1** and **2** with

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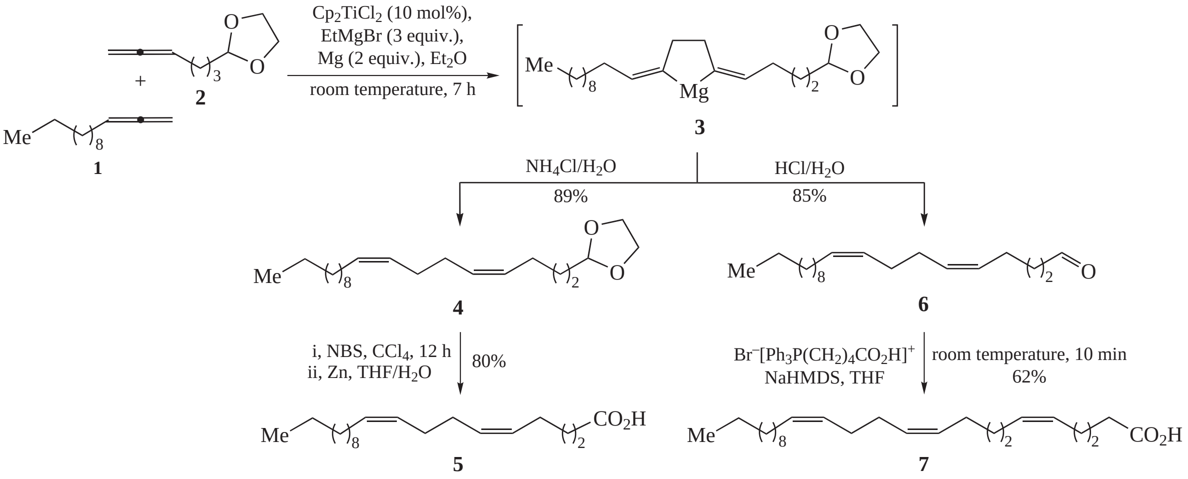
† All reactions were carried out under inert atmosphere. Dichloromethane was distilled from P_2O_5 prior to use. The ether solvents were dried over Na. Commercially available Dess–Martin periodinane and Cp_2TiCl_2 (Aldrich) were used as purchased. One- (^{1}H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-400 instrument [(400.13 MHz (^{1}H), 100.62 MHz (^{13}C)].

Cross-cyclomagnesiation of trideca-1,2-diene and 2-(hexa-4,5-dien-1-yl)-1,3-dioxolane with EtMgBr in the presence of Mg metal and Cp_2TiCl_2 catalyst. Diethyl ether (30 ml), trideca-1,2-diene **1** (0.86 g, 4.8 mmol), 2-(hexa-4,5-dien-1-yl)-1,3-dioxolane **2** (0.62 g, 4.0 mmol), EtMgBr (8 ml of a 1.5 M solution in Et_2O), Mg powder (0.19 g, 8 mmol), and Cp_2TiCl_2 (0.10 g, 0.40 mmol) were placed in a glass reactor with stirring under argon (~0 °C). The reaction mixture was brought to room temperature (20–22 °C) and stirred for 7 h. Then the mixture was treated with either 10% aqueous HCl (20 ml) to give aldehyde **6** or a saturated aqueous solution of NH_4Cl (20 ml) to give dioxolane **4**. The product was extracted with diethyl ether (2×100 ml). The organic phase was separated from water, dried over $MgSO_4$, and filtered. The ether was distilled off *in vacuo* and the residue was chromatographed on a column filled with silica gel (hexane–EtOAc, 30 : 1).



Scheme 2

EtMgBr in the presence of Mg metal and Cp_2TiCl_2 (10 mol%); acid hydrolysis of the reaction mixture gave (5*Z*,9*Z*)-eicosa-5,9-dienal **6** in ~85% yield (see Scheme 2).[†] At the final step, aldehyde **6** was reacted with phosphonium ylide generated from (4-carboxybutyl)triphenylphosphonium bromide on treatment with sodium hexamethyldisilazide (NaHMDS) in THF[22] to furnish (5*Z*,10*Z*,14*Z*)-pentacosa-5,10,14-trienoic acid **7** in ~53% yield.[‡]

The structures of synthesized compounds **4**–**7** were established by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy using 2D heteronuclear correlation experiments (HSQC, HMBC). The *cis*-configuration of substituents at the double bonds in the resulting 1,5-dienes is supported by the presence of high-field signals (~27 ppm) for the internal allylic carbon atoms in the ^{13}C NMR spectrum, indicating the presence of *cis*-interaction with the external allylic carbons.[23]

In conclusion, we have improved the method for the stereoselective synthesis of an efficient human topoisomerase I inhibitor, (5*Z*,9*Z*)-eicosadienoic acid, and developed an original protocol for preparation of previously unknown (5*Z*,10*Z*,14*Z*)-pentacosa-5,10,14-trienoic acid. The new Ti-catalyzed cross-cyclomagnesiation of oxygenated and aliphatic 1,2-dienes induced by Grignard reagents was used as the key stage of the synthesis. In our opinion, the developed synthetic protocols bear a huge potential for the preparation of stereochemically pure di- and trienoic acids upon variation of the structure and the length of the hydrocarbon group of the starting aliphatic and oxygenated 1,2-dienes. Our findings can be useful for the preparation of block synthons in the synthesis of bismethylene-separated polyenes otherwise difficult to prepare.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2017.05.005.

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*2-[(4*Z*,8*Z*)-Nonadeca-4,8-dien-1-yl]-1,3-dioxolane* **4**. Yield 89%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, OMe, *J* 7 Hz), 1.25–1.42 (m, 16H, CH_2), 1.51–1.53 (m, 2H, CH_2), 1.68–1.71 (m, 2H, CH_2), 2.03–2.10 (m, 8H, =CH–CH_2), 3.85–4.00 (m, 4H, CH_2), 4.87 (t, 1H, CH, *J* 5 Hz), 5.38–5.43 (m, 4H, =CH). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 130.4 (CH), 129.8 (CH), 129.6 (CH), 129.1 (CH), 104.6 (CH), 64.8 (2C, CH_2), 33.5 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (2C, CH_2), 29.6 (CH_2), 29.4 (2C, CH_2), 27.4 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 24.0 (CH_2), 22.7 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 336 $[M]^+$. Found (%): C, 78.39; H, 11.94. Calc. for $C_{22}H_{40}O_2$ (%): C, 78.51; H, 11.98.

*(5*Z*,9*Z*)-Eicosa-5,9-dienal* **6**. Yield 85%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, Me, *J* 7 Hz), 1.24–1.48 (m, 16H, CH_2), 1.68–1.72 (m, 2H, CH_2), 2.04–2.10 (m, 8H, =CH–CH_2), 2.42–2.45 (m, 2H, O=CH–CH_2), 5.33–5.42 (m, 4H, =CH), 9.76 (m, 1H, O=CH). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 202.3 (CH), 130.6 (CH), 130.5 (CH), 128.8 (CH), 128.6 (CH), 43.3 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (2C, CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 27.4 (2C, CH_2), 27.2 (CH_2), 26.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 292 $[M]^+$. Found (%): C, 81.99; H, 12.34. Calc. for $C_{20}H_{36}O$ (%): C, 82.12; H, 12.41.

*(5*Z*,9*Z*)-Eicosa-5,9-dienoic acid* **5**. All analytical data recorded for compound **5** were in full accordance with previously published data.[15]

[‡] *(5*Z*,10*Z*,14*Z*)-Pentacosa-5,10,14-trienoic acid* **7**. Sodium bis(trimethylsilyl)amide (2.5 ml, 5 mmol) was added to a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (0.75 g, 1.5 mmol) in anhydrous THF (50 ml) under argon. The reaction mixture was stirred for 10 min at room temperature before adding alkadienal **6** (0.44 g, 1.5 mmol). After stirring for more 2 h at ambient temperature, the mixture was quenched with ammonium chloride solution (20 ml, 10% w/v) and extracted with dichloromethane (40 ml). The organic layer was washed with water (2×50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on a column with silica gel (hexane–EtOAc, 10:1), yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, Me, *J* 7 Hz), 1.25–1.48 (m, 18H, CH_2), 1.66–1.69 (m, 2H, CH_2), 2.05–2.10 (m, 12H, =CH–CH_2), 2.36–2.39 (m, 2H, CH_2), 5.38–5.41 (m, 6H, =C*H*). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 179.4 (CO_2H), 130.4 (CH), 130.2 (CH), 129.9 (CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 33.9 (CH_2), 31.9 (CH_2), 29.1–29.7 (7C, CH_2), 27.4 (CH_2), 27.4 (2C, CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 24.3 (CH_2), 22.7 (CH_2), 14.1 (Me). MS (MALDI-TOF), *m*/*z*: 376 $[M]^+$. Found (%): C, 79.61; H, 11.72. Calc. for $C_{25}H_{44}O_2$ (%): C, 79.73; H, 11.77.

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