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Improved enantioselective synthesis of natural striatenic acid and its methyl ester

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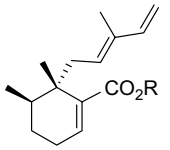
Abstract—This letter describes the improved and efficient enantioselective synthesis of natural striatenic acid, isolated from *Cheilolejeunea serpentina*, and its methyl ester starting from a readily available enantiopure building block.

In 2000, Tori and his collaborators reported the isolation of striatenic acid (+)-**1**, which was obtained from the liverwort *Cheilolejeunea serpentina* collected in Malaysia.[1] They determined the structure and absolute configuration of this striatane-type sesquiterpene by the synthesis of the corresponding optically active methyl ester (+)-**2** (Fig. 1). However, though this synthesis is suitable for the characterization of the natural product, it suffers from low yields at crucial steps and requires the use of $AgNO_3$-impregnated silica gel column chromatography for the separation of undesired stereoisomers.

As part of our research program on the total synthesis of cyclofarnesane skeleton sesquiterpenoids,[2] we describe here an improved enantioselective synthesis of natural striatenic acid (+)-**1** and its methyl ester (+)-**2**. Our straightforward approach of this rearranged cyclofarnesane scaffold is considerably more efficient than the previous one and avoids the stereochemical problem of that route. Our synthetic plan is outlined in Scheme 1. The starting material is the readily available[3] enone (+)-**3**. Conjugate addition of organocopper reagents to 3,4-dimethyl cyclohexenones is well documented and proceeds with the generation of *cis*-vicinal methyls.[4] Thus, exposure of (+)-**3** to the 1,4-addition of magnesium vinylcuprate, followed by quenching with methyl cyanoformate[5] in hexamethylphosphoric triamide afforded **4** as a mixture of highly enolizable β-keto esters in 74% yield. Among four possible diastereomers, reduction of crude **4** with $NaBH_4$ afforded, for the most part, the separable diastereomeric carbomethoxy alcohols **5a**/**5b** (3:2) in 85% yield.[6] Since the stereochemistry of the two newly generated stereogenic centres in **5a**/**5b** is of no significance for the final goal and will be extinguished later, a convenient three-step procedure was then carried out directly on **5a**/**5b** mixture to furnish the key carbomethoxy aldehyde (+)-**6** in 56% overall yield through sequential mesylation of the hydroxyl functionality, ozonolysis of the terminal olefin and DBU-promoted elimination.[7,8]



(+)-**1** R = H
(+)-**2** R = Me

Figure 1.

Wittig olefination of (+)-**6** with the α-methoxy substituted ylid, obtained by reacting methoxymethyltriphenyl-phosphonium chloride[9] with *tert*-BuOK in THF, provided **7** as a mixture of stereoisomers in 62% yield. Subsequently, hydrolysis at 0 °C with 1 M HCl (THF/H_2O) afforded carbomethoxy aldehyde (+)-**8** in 91% yield.[7] Exposure of (+)-**8** to the commercially available 2-(triphenyl-phosphoranylidene) propionaldehyde stereoselectively gave the extended carbon chain

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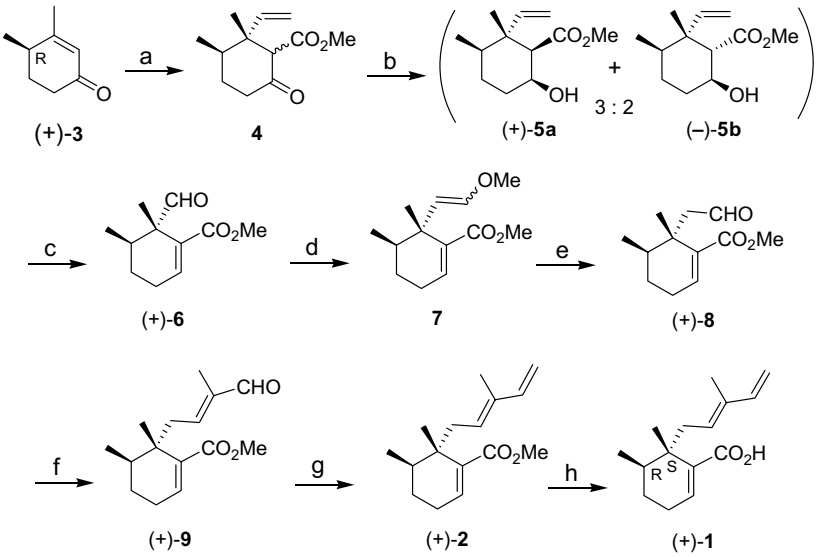

Scheme 1. Reagents and conditions: (a) CH_2=CHMgBr, CuBr·SMe_2, THF, −78 °C then HMPA and $NCCO_2Me$, −78 °C to rt, 74%; (b) $NaBH_4$, MeOH, −40 °C to rt, 85%; (c) (i) MsCl, pyridine; (ii) O_3, CH_2Cl_2, −78 °C; SMe_2; (iii) DBU, benzene, reflux, 56% for three steps; (d) $Ph_3P^+CH_2OMeCl^-$, *tert*-BuOK, THF, rt, 62%; (e) 1 M HCl/THF 1:2, 0 °C, 91%; (f) Ph_3P=$C(CH_3)CHO$, toluene, reflux, 84%; (g) $Ph_3P^+MeI^-$, *tert*-BuOK, toluene, rt, 93%; (h) 1 M KOH/MeOH 1:1, 65 °C, 85%.

E-α,β-unsaturated carbomethoxy aldehyde (+)-**9** as a single stereoisomer in 84% yield.[7] At this stage, methylenation of (+)-**9** with the salt-free Wittig reagent, prepared from methyltriphenyl-phosphonium iodide and *tert*-BuOK, provided the methyl ester of striatenic acid (+)-**2** in 93% yield. The spectroscopic data (^{1}H and ^{13}C NMR) of (+)-**2** matched those reported in the literature[1,7] and the specific rotation[10] was the same in magnitude and in sign [α_D^{25} +51.0 (*c* 1, $CHCl_3$)/lit.[1] [$\alpha]_D^{20}$ +49.9 (*c* 0.8, $CHCl_3$)]. Finally, saponification of (+)-**2** using 1 M KOH/MeOH at 65 °C afforded the crystalline target molecule (+)-**1** (mp 106 °C) in 85% yield. The ^{1}H and ^{13}C NMR spectra of our synthetic sample were in complete agreement with those of the literature, but the specific rotation [[$\alpha]_D^{25}$ +36.0 (*c* 1, $CHCl_3$)] was slightly different in magnitude [lit.[1] [$\alpha]_D^{20}$ +43.5 (*c* 2.7, $CHCl_3$)], probably due to the high purity of our sample. The crystalline nature of natural striatenic acid has not been reported in the original isolation from the liverwort *C. serpentina*.

In conclusion, we have presented a highly efficient synthetic route to striatenic acid via the corresponding methyl ester. The target molecule (+)-**1** was prepared from a versatile enantiopure building block by a 10-step sequence in 14% overall yield (9-step sequence in 16% overall yield for (+)-**2**). We believe that our strategy compares favourably with the one described[1] as far as stereoselectivity, chemical yields and high purity of the crystalline target molecule are concerned. The application of this methodology to the synthesis of other rearranged cyclofarnesane skeleton sesquiterpenoïds is in progress and will be given in due course.

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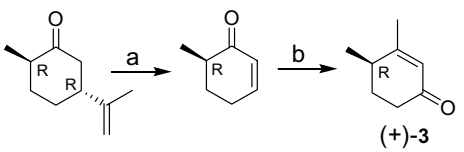
3. Obtained in two steps from (+)-(2*R*,5*R*)-*trans*-dihydrocarvone, conveniently separated by column chromatography from its minor *cis*-isomer starting from the commercial Aldrich mixture (hexane/ether 6:1). Eq. 1 (a) Ozonolysis in methanol and then treatment with $Cu(OAc)_2/FeSO_4$ led to (+)-(*R*)-6-methylcyclohex-2-en-1-one (Solladié, G.; Hutt, J. *J. Org. Chem.* **1987**, *52*, 3560–3566); (b) Treatment of this ketone with methyllithium, followed by oxidation with pyridinium chlorochromate (PCC), afforded (+)-**3** (Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun.* **1987**, 358–359; See also: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685).



(1)

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6. At this stage, and before the next three-step sequence, an aliquot of the **5a/5b** mixture was carefully separated by column chromatography on silica gel and analyzed in order to confirm the expected gross structures. Assignment of the complete stereochemistry as showed in Scheme 1 was deduced on the basis of the connectivities observed in COSY and NOESY experiments. Compound (+)-**5a**. $[\alpha]_D^{25}$ +43.0 (*c* 1, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 5.58 (dd, $J = 17.4$, 10.7 Hz, 1H), 4.99 (dd, $J = 10.7$, 1.1 Hz, 1H), 4.86 (dd, $J = 17.4$, 1.1 Hz, 1H), 4.14 (q, $J = 2.3$ Hz, 1H), 3.91 (d, $J = 2.3$ Hz, 1H), 3.59 (s, 3H), 2.33 (d, $J = 2.3$ Hz, 1H), 1.90 (dq, $J = 14.0$, 3.5 Hz, 1H), 1.68 (qd, $J = 13.5$, 3.6 Hz, 1H), 1.44 (tt, $J = 13.7$, 3.6 Hz, 1H), 1.39–1.32 (m, 2H), 1.13 (s, 3H), 0.75 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6 (C), 147.5 (CH), 112.6 (CH_2), 66.8 (CH), 54.6 (CH), 51.0 (CH_3), 42.9 (C), 40.1 (CH), 31.6 (CH_2), 24.2 (CH_2), 16.3 (CH_3), 12.3 (CH_3). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.12; H, 9.47. Compound (−)-**5b**. Mp = 62 °C, $[\alpha]_D^{25}$ −17.0 (*c* 1, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 6.25 (dd, $J = 17.4$, 11.1 Hz, 1H), 5.02 (dd, $J = 11.1$, 0.8 Hz, 1H), 4.98 (dd $J = 17.4$, 0.8 Hz, 1 Hz, 1H), 4.09 (td, $J = 10.4$, 4.8 Hz, 1H), 3.69 (s, 3H), 2.48 (d, $J = 10.4$ Hz, 1H), 1.90 (tt, $J = 13.8$, 4.3 Hz, 1H), 1.85–1.76 (m, 2H), 1.62 (br s, 1H), 1.51 (tdd, $J = 13.1$, 11.0, 4.1 Hz, 1H), 1.39 (dq, $J = 13.8$, 3.2 Hz, 1H), 1.05 (s, 3H), 1.01 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (C), 143.5 (CH), 112.6 (CH_2), 68.6 (CH), 55.8 (CH), 51.2 (CH_3), 42.7 (C), 37.1 (CH), 28.3 (CH_2), 26.9 (CH_2), 25.1 (CH_3), 14.7 (CH_3). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.07; H, 9.53.
7. All new compounds were fully characterized spectroscopically and had satisfactory microanalyses. Selected data: Compound (+)-**6**. Mp = 54 °C, $[\alpha]_D^{25}$ +41.0 (*c* 1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.22 (t, $J = 4.0$ Hz, 1H), 3.69 (s, 3H), 2.32–2.25 (m, 2H), 1.76 (dqd, $J = 12.2$, 6.8, 3.0 Hz, 1H), 1.71–1.59 (m, 1H), 1.45–1.34 (m, 1H), 1.12 (s, 3H), 0.80 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5 (CH), 166.7 (C), 143.5 (CH), 133.2 (C), 51.8 (CH_3), 51.0 (C), 31.6 (CH), 26.0 (CH_2), 24.9 (CH_2), 15.4 (CH_3), 13.5 (CH_3). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.56; H, 8.19. Compound (+)-**8**. $[\alpha]_D^{25}$ +118 (*c* 1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (dd, $J = 4.1$, 1.5 Hz, 1H), 7.05 (t, $J = 3.9$ Hz, 1H), 3.70 (s, 3H), 3.18 and 2.55 (ABX, $J = 16.0$, 4.1, 1.5 Hz, 2H), 2.24–2.17 (m, 2H), 1.70 (dqd, $J = 10.8$, 6.8, 3.0 Hz, 1H), 1.58–1.40 (m, 2H), 1.16 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4 (CH), 167.4 (C), 141.9 (CH), 135.8 (C), 51.5 (CH_3), 50.0 (CH_2), 38.3 (C), 36.7 (CH), 25.7 (CH_2), 25.6 (CH_2), 20.9 (CH_3), 15.4 (CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.68. Compound (+)-**9**. $[\alpha]_D^{25}$ +44.0 (*c* 1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.00 (t, $J = 3.9$ Hz, 1H), 6.27 (ddq, $J = 8.4$, 6.2, 1.3 Hz, 1H), 3.66 (s, 3H), 3.03 (ddq, $J = 16.3$, 6.2, 1.1 Hz, 1H), 2.60 (dd, $J = 16.3$, 8.4 Hz, 1H), 2.21–2.13 (m, 2H), 1.71 (br s, 3H), 1.64–1.39 (m, 3H), 1.19 (s, 3H), 0.90 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (CH), 167.4 (C), 152.1 (CH), 142.2 (CH), 140.4 (C), 136.2 (C), 51.4 (CH_3), 40.0 (C), 35.8 (CH_2), 35.3 (CH), 25.7 (CH_2), 25.6 (CH_2), 20.9 (CH_3), 15.6 (CH_3), 9.4 (CH_3). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.31; H, 8.89. Compound (+)-**2**. $[\alpha]_D^{25}$ +51.0 (*c* 1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (t, $J = 3.9$ Hz, 1H), 6.32 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.24 (br t, $J = 7.2$ Hz, 1H), 5.03 (d, $J = 17.4$ Hz, 1H), 4.88 (d, $J = 10.8$ Hz, 1H), 3.66 (s, 3H), 2.73 and 2.40 (ABX, $J = 15.5$, 8.3, 6.1 Hz, 2H), 2.18–2.09 (m, 2H), 1.71 (s, 3H), 1.69–1.61 (m, 1H), 1.55–1.46 (m, 1H), 1.39–1.35 (m, 1H), 1.15 (s, 3H), 0.89 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9 (C), 141.8 (CH), 140.8 (CH), 137.3 (C), 135.1 (C), 130.0 (CH), 110.2 (CH_2), 51.2 (CH_3), 40.0 (C), 34.9 (CH_2), 34.5 (CH), 25.9 (CH_2), 25.6 (CH_2), 20.9 (CH_3), 15.7 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.09; H, 9.78. Compound (+)-**1**. Mp = 106 °C, $[\alpha]_D^{25}$ +36.0 (*c* 1, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (t, $J = 3.9$ Hz, 1H), 6.31 (dd, $J = 17.4$, 10.6 Hz, 1H), 5.28 (br t, $J = 7.5$ Hz, 1H), 5.03 (d, $J = 17.4$ Hz, 1H), 4.88 (d, $J = 10.6$ Hz, 1H), 2.83 and 2.40 (ABX, $J = 15.7$, 8.8, 6.1 Hz, 2H), 2.21–2.15 (m, 2H), 1.75 (s, 3H), 1.73–1.61 (m, 1H), 1.55–1.36 (m, 2H), 1.15 (s, 3H), 0.89 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (C), 144.1 (CH), 141.8 (CH), 136.4 (C), 135.1 (C), 130.0 (CH), 110.3 (CH_2), 39.9 (C), 34.7 (CH_2), 34.6 (CH), 25.9 (CH_2), 25.8 (CH_2), 20.7 (CH_3), 15.7 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.53; H, 9.49.
8. Direct transformation of the β-ketoester into α,β-unsaturated ester using Cp_2ZrHCl (Schwartz reagent) was unfitted for our synthetic sequence [Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1992**, *33*, 7461–7464].
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10. The high enantiomeric purity of (+)-**2** was verified by chiral HPLC [>98% ee; Chiralpak AD (250 × 4.6 mm) column, hexane, 1 mL/min].