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Synthesis of (+)-striatene: confirmation of its stereostructure

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ABSTRACT

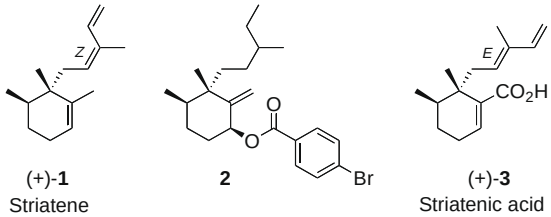
The first enantioselective synthesis of natural striatene (+)-**1**, isolated from liverwort *Ptychanthus striatus*, starting from commercially available (*R*)-Pulegone is described. Its stereostructure was confirmed by X-ray analysis of a 3,5-dinitrobenzoate derivative obtained from a key intermediate and its high optical purity was verified by chiral HPLC.

Numerous isolated terpenoids from liverworts possess interesting biological activity.[1] Some of them have characteristic scents, pungency and bitterness, others exhibit bioactivities and medicinal properties.[2] Takeda and his collaborators reported the isolation of striatene (+)-**1**, which was obtained from liverwort *Ptychanthus striatus*.[3] Its structure has been established by spectroscopic analysis, and the absolute configuration by the CD exciton chirality method performed on benzoate derivative **2** prepared in 8 mg by chemical modification of striatene (+)-**1** (Fig. 1). Up to date, no racemic or enantioselective approach of striatene **1** has been developed.

As part of our research programme on the enantioselective synthesis of cyclofarnesane skeleton sesquiterpenoids,[4] we recently reported the synthesis of natural striatenic acid (+)-**3** isolated from *Cheilolejeuna serpentina* (Fig. 1).[5] Following our interest concerning the synthesis of rearranged cyclofarnesane products, we present here the first enantioselective total synthesis of natural striatene (+)-**1** in order to confirm its stereostructure. The thermodynamically unstable *Z*-double bond stereochemistry of the C6 side chain in striatene (+)-**1** led us to develop a new synthetic methodology. Our synthetic plan is outlined in Scheme 1.

The chiral information was already encoded in the commercially available starting material, (*R*)-Pulegone (+)-**4**. Conversion of (*R*)-Pulegone into the thermodynamic silyl enol ether (+)-**5** was achieved in three steps in a 59% yield following a reported procedure.[6] This non-racemic chiral building block was recently used for the synthesis of *ent*-agelasine F.[7] First, we studied the alkylation of the in situ generated enolate from (+)-**5**, with the halogenated derivative possessing the entire carbon framework with the required *Z*-double bond. Unfortunately, all attempts in order to prepare the (*Z*)-5-chloro- or (*Z*)-5-bromo-3-methylpenta-1,3-diene in a pure form failed.[8] As a consequence, we turned our efforts to synthesize another bromo derivative, (*Z*)-5-bromo-3-methylpent-3-en-1-yne.[9] Then, regeneration of the thermodynamic enolate by treatment with methyllithium, and enolate alkylation with this brominated chain provided a mixture of the diastereomeric alkylated compounds (+)-**6a** and (+)-**6b** in a high total yield in favour of the desired isomer (+)-**6a** (85:15 ratio).

After having conveniently separated these two stereoisomers[10] by column chromatography (73% yield for (+)-**6a**), first attempts to reduce the triple bond of the major compound (+)-**6a** by using standard methods failed (H_2, Pd/$CaCO_3$ lead-poisoned or H_2, Pd/$BaSO_4$ quinoline-poisoned). Indeed, no reaction was observed and the unreacted starting material was recovered. Then, we focused our attention by using a hydrometallation methodology. Hydrozirconation[11] using $HZrCp_2Cl$ (Schwartz reagent) generated in situ by reaction of $ZrCp_2Cl_2$ and Dibal-H as the hydride source



(+)-**1** Striatene — **2** — (+)-**3** Striatenic acid

Figure 1. Structures of striatene (+)-**1**, **2** and striatenic acid (+)-**3**.

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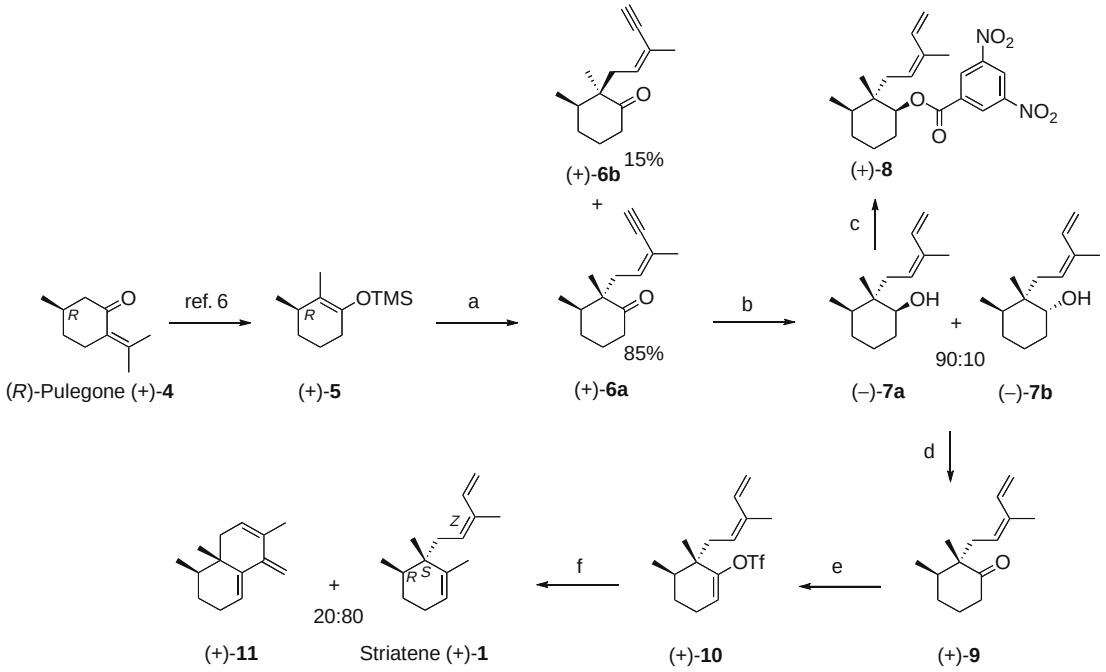

Scheme 1. Reagents and conditions: (a) MeLi, Et_2O, −20 °C to rt, 1 h then (*Z*)-5-bromo-3-methylpent-3-en-1-yne, THF, HMPA, −80 °C–rt, 12 h, 73%; (b) $ZrCp_2Cl_2$, Dibal-H, THF/toluene 3:1, 0 °C, 81%; (c) 3,5-dinitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h, 91%; (d) TPAP (cat.), NMO, CH_2Cl_2, 4 Å MS, 0 °C–rt, 4 h, 86%; (e) LiHMDS, THF, −80 °C, 1 h then $PhNTf_2$, THF, −80 °C–rt, 12 h, 83%; (f) Me_2Zn, $Pd(PPh_3)_4$, THF, 0 °C–rt, 12 h, 71%.

afforded the diastereomeric alcohols (−)-**7a** and (−)-**7b** (90:10 ratio) in an 89% yield. The stereochemistry of the newly generated stereogenic centre in **7a**/**7b** is of no signification for the final goal. At this stage, an aliquot of **7a**/**7b** mixture was separated by column chromatography on silica gel and the stereostructure of pure (−)-**7a** was unequivocally determined by single crystal X-ray crystallography of the corresponding 3,5-dinitrobenzoate derivative[12] (+)-**8** (Fig. 2).

Oxidation of the mixture **7a**/**7b** with catalytic tetrapropylammonium perruthenate (TPAP)[13] and NMO as the co-oxidant gave (+)-**9** in 86% yield. Then, methyllithium was added to the ketone (+)-**9** at 0 °C in Et_2O affording the corresponding tertiary alcohol in 91% yield. Regioselective elimination using different reagents (HCO_2H, TFA, H_2SO_4, $SOCl_2$ or $POCl_3$/pyridine) gave as best result an isomeric mixture containing a 2:1 ratio of endocyclic:exocyclic double bonds which were inseparable, in a 70% yield.

In order to prevent the formation of the inseparable *exo* methylene isomer, we decided to use palladium-catalyzed cross-coupling reaction with vinyl triflate (+)-**10** and organometallic reagent. Therefore, compound (+)-**9** was transformed into a vinyl triflate by treatment with LiHMDS followed by addition of $PhN(Tf)_2$ (Comins reagent) affording (+)-**10** in 83% yield.[14] In a first attempt, the palladium-catalyzed cross-coupling reaction of vinyl triflate (+)-**10** with trimethylindium[15] in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ afforded a 18:22 mixture of natural striatene (+)-**1** and the bicyclic compound (+)-**11** resulting from an intramolecular 6-exo Heck reaction in 95% yield. Encouraged by this first result, we tried to invert the selectivity of this coupling reaction and turned our attention to modify the organometallic reagent. Negishi coupling methylation[16] with dimethylzinc in the presence of $Pd(PPh_3)_4$ was accomplished in 88% yield and a 20:80 molar ratio in favour of natural striatene (+)-**1**. Purification of these two organic compounds by $AgNO_3$-impregnated silica gel column chromatography gave pure striatene (+)-**1** in 71% yield. The IR, ^1H and ^{13}C NMR spectra of our synthetic sample were in complete agreement with those in the literature. The high optical purity of striatene (+)-**1** was confirmed by chiral HPLC (ee >95%). However, the magnitude of the specific rotation of striatene (+)-**1** {$[\alpha]_D^{25}$ +60.3 (*c* 1, $CHCl_3$)} disagreed with that given in the literature[3] {$[\alpha]_D^{25}$ +72.7 (*c* 1.19, $CHCl_3$)}, probably due to an artefact during the extractive processes of the natural product.

In conclusion, the first asymmetric synthesis of striatene (+)-**1** has been accomplished in a short and stereoselective fashion from a commercially available chiral building block, (*R*)-Pulegone, which unambiguously confirms its absolute stereochemistry. In addition, the enantiomer (−)-striatene can be synthesized from the available (*S*)-Pulegone, following the reaction sequence detailed above.

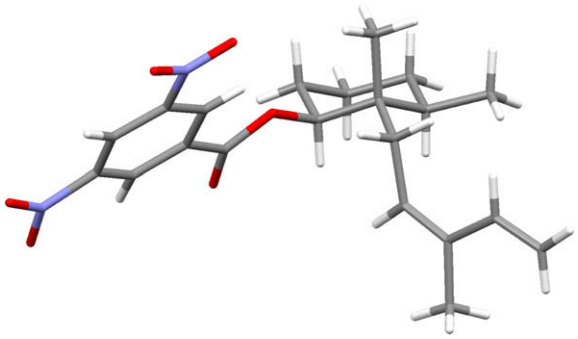

Figure 2. ORTEP projection of the molecular structure of 3,5-dinitrobenzoate (+)-**8**.

Acknowledgements

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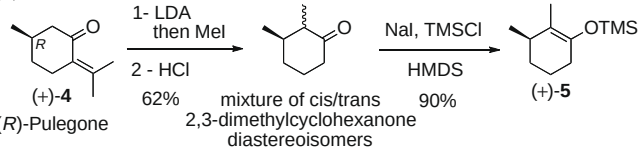
6. Silyl enol ether (+)-**5** was synthesized from commercially available (*R*)-Pulegone (+)-**4** according to the literature: (a) Formation of an enantiopure cis/trans mixture of 2,3-dimethylcyclohexanone: methylation see Tori, M.; Uchida, N.; Sumida, A.; Furuta, H.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1513–1517 and acid-induced retro aldolisation see Dagneau, P.; Canonne P. *Tetrahedron: Asymmetry* **1996**, *7*, 2817–2820; (b) Formation of silyl enol ether (+)-**5**: Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett.* **1998**, *39*, 4347–4350.



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9. Rearrangement of commercially available 3-methyl-1-penten-4-yn-3-ol under acidic conditions as described in the literature (Cymerman, J.; Heilbron, I. M.; Jones, E. R. H. *J. Chem. Soc.* **1945**, 90–94) afforded a *Z*/*E* mixture of 3-methylpent-4-en-1-yn-3-ol in favour of the *Z*-stereoisomer (85:15 by GC). The major *Z*-stereoisomer was easily isolated in pure form by fractional distillation of the mixture through a spinning band.
10. All new compounds were fully characterized spectroscopically. Representative spectra data for some new compounds: *Compound* (+)-**6a**. $[\alpha]_D^{25}$ +82.5 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 7.7 Hz, 3H), 1.00 (s, 3H), 1.47–1.71 (m, 2H), 1.82 (br q, *J* = 1.5 Hz, 3H), 1.74–1.98 (partially overlapped m, 3H), 2.26–2.44 (m, 2H), 2.45–2.61 (m, 2H), 3.08 (s, 1H), 5.69 (br t, *J* = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 18.8, 23.2, 24.5, 29.4, 37.3, 38.5, 39.2, 52.5, 80.8, 83.4, 118.7, 136.1, 215.8. HRMS (ESI) calcd for $C_{14}H_{21}O$: 205.1587 ($M+H^+$); found 205.1578. *Compound* (+)-**6b**. $[\alpha]_D^{25}$ +72.0 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, *J* = 7.7 Hz, 3H), 1.09 (s, 3H), 1.62–1.73 (m, 2H), 1.81 (br s, 3H), 1.75–1.84 (partially overlapped m, 1H), 2.24–2.33 (m, 3H), 2.48–2.58 (m, 2H), 2.79 (dd, *J* = 14.8, 7.5 Hz, 1H), 3.12 (s, 1H), 5.52 (br t, *J* = 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.9, 20.2, 23.2, 25.8, 29.6, 33.4, 38.7, 43.4, 52.7, 81.3, 83.1, 119.6, 134.3, 215.7. HRMS (ESI) calcd for $C_{14}H_{21}O$: 205.1587 ($M+H^+$); found 205.1577. *Compound* (−)-**7a**. Mp = 49 °C, $[\alpha]_D^{25}$ −17.4 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 1.20–1.26 (m, 1H), 1.28–1.37 (m, 2H), 1.40–1.49 (m, 2H), 1.62–1.70 (m, 2H), 1.86 (br q, *J* = 1.0 Hz, 3H), 2.06 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.52 (dd, *J* = 14.9, 8.7 Hz, 1H), 3.41 (dd, *J* = 11.2, 4.1 Hz, 1H), 5.11 (br d, *J* = 10.8 Hz, 1H), 5.23 (br d, *J* = 17.4 Hz, 1H), 5.51 (t, *J* = 8.3 Hz, 1H), 6.92 (ddd, *J* = 17.4, 10.8, 0.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 15.5, 20.4, 24.2, 30.1, 30.8, 33.9, 36.0, 42.7, 74.1, 114.1, 127.0, 133.8, 134.4. HRMS (ESI) calcd for $C_{14}H_{25}ONa$: 231.1719 ($M+Na^+$); found 231.1721. *Compound* (−)-**7b**. $[\alpha]_D^{25}$ −21.8 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 1.18–1.30 (m, 1H), 1.38–1.47 (m, 2H), 1.51–1.57 (m, 2H), 1.59–1.63 (m, 1H), 1.64–1.67 (m, 1H), 1.74–1.81 (m, 1H), 1.85 (br q, *J* = 1.1 Hz, 3H), 2.22 (dd, *J* = 15.0, 7.8 Hz, 1H), 2.30 (dd, *J* = 15.0, 8.5 Hz, 1H), 3.57 (br s, 1H), 5.11 (br d, *J* = 10.8 Hz, 1H), 5.23 (br d, *J* = 17.3 Hz, 1H), 5.55 (br t, *J* = 8.3 Hz, 1H), 6.87 (ddd, *J* = 17.3, 10.8, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 17.1, 20.1, 20.4, 29.0, 30.4, 34.4, 35.2, 40.9, 73.0, 114.2, 127.6, 133.6, 134.0. HRMS (ESI) calcd for $C_{14}H_{24}ONa$: 231.1719 ($M+Na^+$); found 231.1717. *Compound* (+)-**9**. $[\alpha]_D^{25}$ +4.9 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.7 Hz, 3H), 0.99 (s, 3H), 1.48–1.96 (partially overlapped m, 5H), 1.79 (br q, *J* = 1.1 Hz, 3H), 2.28–2.45 (m, 3H), 2.53 (ddd, *J* = 14.9, 6.6, 1.0 Hz, 1H), 5.08 (br d, *J* = 10.8 Hz, 1H), 5.19 (br d, *J* = 17.3 Hz, 1H), 5.27 (br t, *J* = 7.4 Hz, 1H), 6.78 (ddd, *J* = 17.3, 10.8, 0.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7, 19.1, 20.2, 24.2, 29.2, 33.9, 38.5, 38.7, 52.6, 113.9, 126.9, 133.7, 133.9, 215.8. HRMS (ESI) calc for $C_{14}H_{23}O$: 207.1743 [$M+H^+$]; found: 207.1737. (+)-Striatene (+)-**1**. $[\alpha]_D^{25}$ + 60.3 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H), 1.39–1.47 (m, 2H), 1.61–1.70 (partially overlapped m, 1H), 1.63 (br q, *J* = 1.4 Hz, 3H), 1.82 (br s, 3H), 1.94–2.01 (m, 2H), 2.17 (br dd, *J* = 15.9, 5.0 Hz, 1H), 2.42 (dd, *J* = 15.9, 8.9 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 5.16–5.22 (partially overlapped m, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.46 (br s, 1H), 6.80 (dd, *J* = 17.4, 10.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 19.4, 20.2, 20.8, 25.5, 27.2, 34.3, 34.3, 40.9, 113.4, 124.6, 128.4, 133.3, 134.2, 139.4. HRMS (ESI) calcd for $C_{15}H_{24}Ag$: 311.0923 [$M+Ag^+$]; found: 311.0922.
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12. Details of the X-ray structure for compound (+)-**8** can be obtained from the Cambridge Crystallographic Data Centre: CCDC 736783. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk]. $C_{21}H_{26}N_2O_6$, M = 402.44 g mol^{-1}. The colourless single crystal (crystal size/mm^3: 0.3 × 0.15 × 0.10) was analyzed at 293 K with a Bruker Nonius Kappa-CCD automated four-circle diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Crystal data: trigonal, space group *P*-32, *a* = 15.888(5) Å, *b* = 15.888(5) Å, *c* = 7.307(5) Å, *V* = 1597.4(13) Å^3, *Z* = 3, *Dx* = 1.255 g/cm^3, *F*(0 0 0) = 642, and μ(Mo-K$_\alpha$) = 0.92 cm^{-1}. 265 parameters were refined on F^2 using 1806 reflections to final indices R^1 [F^2 >4σ(F^2)] = 0.0559, $wR_2[(w = 1/[\sigma^2(F_o^2) + (0.0535P)^2 + 0.3592P)$ where $P = (F_o^2 + 2F_c^2)/3] = 0.1193$. Residual Fourier/e Å^{-3}: −0.196; 0.162.
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