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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7381–7384

Chemoenzymatic syntheses of the linear triquinane-type sesquiterpenes (+)-hirsutic acid and (−)-complicatic acid

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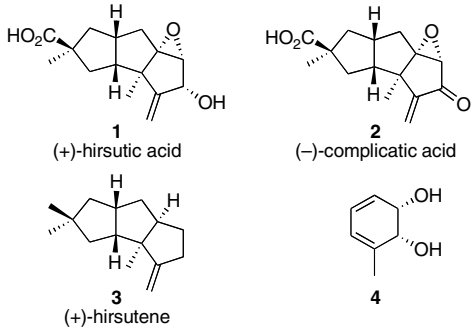
Received 11 July 2006; accepted 28 July 2006
Available online 28 August 2006

Abstract—Formal total syntheses of the natural enantiomeric forms of the title sesquiterpenes **1** and **2** have been achieved using, as starting material, the readily available and enantiomerically pure *cis*-1,2-dihydrocatechol **4** derived from the whole-cell biotransformation of toluene.

In 1947, Heatley and co-workers reported that (+)-hirsutic acid C [**1**, also known as (+)-hirsutic acid] is the major metabolite produced by the filamentous fungus *Stereum hirsutum* and at this time they established the molecular formula $C_{15}H_{20}O_4$ for the compound.[1] Using various spectroscopic techniques, Scott et al. deduced its structure in 1965[2] and this was then confirmed through X-ray analysis of the *p*-bromophenacyl ester derivative.[3] The related linear triquinane-type sesquiterpene (−)-complicatic acid (**2**) was first isolated in 1973 from the fungus *Stereum complicatum* that also produces isolable quantities of what proved to be its biogenetic precursor, namely (+)-hirsutic acid (**1**).[4] This is, in turn, likely to be derived, in vivo, from the triquininoid hydrocarbon (+)-hirsutene (**3**) that has been found as a metabolite of the basidiomycete *Coriolus consors*.[5] Compound **2** shows moderate biological activity against a range of Gram-positive and Gram-negative bacteria as well as certain fungi.[4,6] It also gives a positive Ames test and conjugates with the amino acid cysteine.[6] Unsurprisingly, congeners **1** and **3** show little comparable activity.

Both compounds **1** and **2** have been the subjects of a number of synthetic studies.[7] Matsumoto[8] and Lansbury[9] reported some preliminary work in the early 1970s with the former researcher establishing, in 1974, the first total synthesis of the racemic modification of complicatic acid (**2**) and also demonstrating that this could be reduced with $NaBH_4$ in ethanol to (±)-hirsutic acid [(±)-**1**].[8b] Subsequent studies by Trost,[10] Ikegami,[11] Greene,[12] Magnus,[13] Schuda[14] and Singh[15] have resulted in the establishment of alternative total syntheses or formal total syntheses of the racemic modifications of the title acids. Ikegami[16] and Greene[17] have each extended their approaches so as to obtain hirsutic acid in enantiomerically enriched form while Sakai and co-workers[18] have developed enzyme-mediated routes to enantiomerically enriched samples of a bicyclo-[3.3.0]octane relevant to the synthesis of hirsutic acid.



The continued isolation of new, highly functionalized and biologically active linear triquinane-type sesquiterpenoids[19] has stimulated the ongoing development of new methods for the production of this class of natural product although most such efforts continue to deliver racemic materials.[20] As part of our own program in this area, we recently reported[21] that the enantiomerically pure and readily available *cis*-1,2-dihydrocatechol **4**,[22]

Keywords: Chemoenzymatic; (−)-Complicatic acid; Diels–Alder reaction; *cis*-1,2-Dihydrocatechol; Sesquiterpene; Triquinane.
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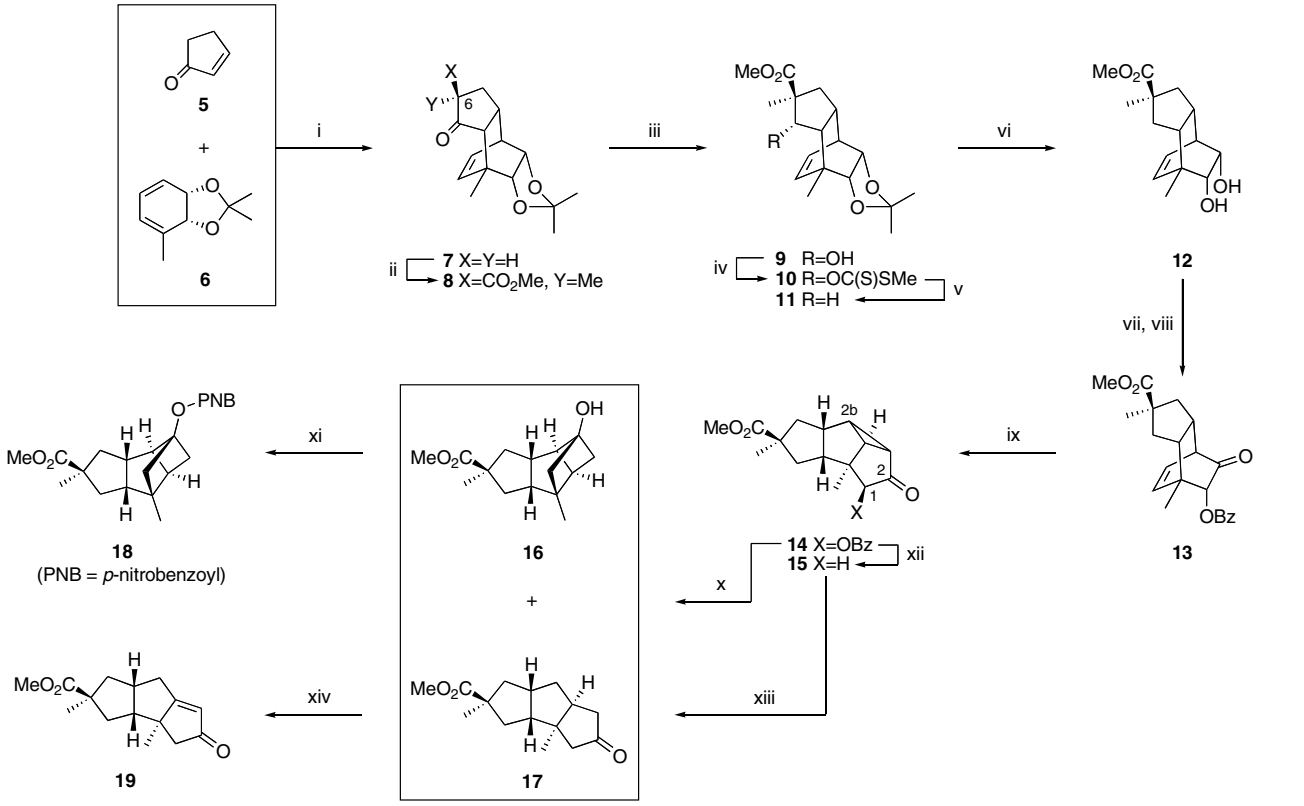
doi:10.1016/j.tetlet.2006.07.145

which is derived from the whole-cell biotransformation of toluene, can be converted into the non-natural enantiomeric or (−)-form of compound **3**. This synthesis exploited Diels–Alder cycloaddition and oxa-di-π-methane rearrangement processes in a reaction sequence first introduced by Demuth[23] as a means for obtaining triquinanes and one that has subsequently been exploited by others for the same purpose.[15,20e] Herein, we report on the exploitation of metabolite **4** in the development of total syntheses of the naturally occurring forms of the title triquinanes.

The reaction sequence leading to a previously prepared precursor of acids **1** and **2** is shown in Scheme 1. Thus, cyclopentenone (**5**) was reacted in a high pressure-promoted (19 kbar) Diels–Alder reaction with the readily prepared[22a] acetonide derivative, **6**, of *cis*-1,2-dihydrocatechol **4**. The steric demands of the acetonide group associated with diene **6** ensure that the dominant mode of cycloaddition involves β-face addition of the dienophile thus leading to adduct **7** (71%) as the major product of the reaction. Treatment of the latter compound with LiHMDS, then with methyl iodide followed by reaction of the intermediate mono-methylated species with the same base and then Mander's reagent[24] affords, in 75% yield, the crystalline ester **8**.[25] Reversing the order of addition of methyl iodide and Mander's reagent in this type of reaction sequence affords C6-*epi*-**8** in 72% yield. Reduction of the ketone residue within compound **8** was achieved under Luche conditions[26] to give alcohol **9** (99%), that is tentatively identified as possessing the illustrated α-configuration at the newly introduced stereogenic centre. The derived xanthate ester **10** was then subjected to a Barton–McCombie reduction[27] with tri-*n*-butyltin hydride in the presence of AIBN and so forming the crystalline compound **11**[25] (95% from **9**). Hydrolysis of the acetonide group within the latter material proved somewhat problematic[28] but could ultimately be achieved in a preparatively useful fashion by heating a water/methanol solution of compound **11** at 80 °C for 3–5 days in the presence of activated DOWEX-50 resin. The resulting diol **12** (76–90%) was then mono-oxidized in a completely regioselective manner with the oxoammonium salt derived from 4-acetamido-TEMPO[29] to give a rather unstable acyloin that was immediately treated with benzoyl chloride in the presence of triethylamine and *N*,*N*-dimethylaminopyridine (DMAP). In this manner, the crystalline benzoate **13**[25] was obtained in 74% yield (from diol **11**). Photolysis of an acetone solution of compound **13** with a medium-pressure mercury lamp for 5 days at 0 °C resulted in an 81% yield of product **14** arising from



Scheme 1. Reagents and conditions: (i) CH_2Cl_2, 19 kbar, 18 °C, 24 h; (ii) LiHMDS, MeI, THF, 0–18 °C, 4 h then LiHMDS, MeO_2CCN, THF, 0–18 °C, 4 h; (iii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0–18 °C, 4 h; (iv) NaHMDS, CS_2, MeI, THF, 0–18 °C, 6 h; (v) *n*-Bu_3SnH, AIBN, toluene, 112 °C, 4 h; (vi) DOWEX-50 resin, MeOH/H_2O, 80 °C, 3–5 days; (vii) 4-AcNH-TEMPO, *p*-TsOH·H_2O, CH_2Cl_2, 0–18 °C, 5 h; (viii) BzCl, Et_3N, DMAP, CH_2Cl_2, 0–18 °C, 18 h; (ix) *hv*, acetophenone, acetone, 0 °C, 5 days; (x) SmI_2, THF/MeOH, −78 to 18 °C, 2 h; (xi) *p*-O_2NBzCl, Et_3N, DMAP, CH_2Cl_2, 18 °C, 3 h; (xii) SmI_2, THF/MeOH, −78 °C, 10 min; (xiii) *n*-Bu_3SnH, AIBN, benzene, 80 °C, 9 h; (xiv) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0–18 °C, 1 h then $Pd(OAc)_2$, MeCN, 18 °C, 15 h, then H_3O^+.

successive oxa-di-π-methane rearrangement and C-1 epimerization steps. Treatment of the latter compound, at −78 to 18 °C, with an excess of samarium(II) iodide afforded, presumably via intermediate **15**, a chromatographically separable mixture of the cyclobutanol **16** (25%) and the triquinane **17** (56%). The former product, the structure of which was established through a single-crystal X-ray analysis of the readily derived *p*-nitrobenzoate **18** (75%),[25] probably arises through reductive cleavage of the cyclopropyl moiety and accompanying coupling of C2 and C2b within compound **15**.[30] Better yields (87%) of the desired product **17** could be obtained using a stepwise reduction process involving treatment of compound **14** with two molar equivalents of SmI_2 at −78 °C, then reaction of the ensuing and isolable keto-ester **15** with tri-*n*-butyltin hydride and AIBN in refluxing benzene. Dehydrogenation of compound **17** so as to give the corresponding enone **19** was achieved using conditions related to those defined by Crimmins and Mascarella during the course of their total synthesis of the angular triquinane (±)-silphinene.[31] Thus, treatment of compound **17** with trimethylsilyl triflate in the presence of 2,6-lutidine gave a 4:1 mixture of the required trimethylsilyl enol ether and its regioisomer. Reaction of this mixture with $Pd(OAc)_2$[32] then afforded, after acidic work-up, a chromatographically separable mixture of enone **19**[33] (85% at 69% conversion) and the starting ketone **17** (31% recovery). Compound **19** represents an advanced intermediate associated with the Ikegami[16b] and Greene[17] syntheses of the title acids, so the acquisition of it by the means just described, constitutes formal total syntheses of both these natural products.

This study, when considered in conjunction with our earlier work,[21] establishes that by controlling the facial selectivity of Diels–Alder reactions involving diene **4**, either enantiomeric form of the linear triquinane framework can be obtained. Furthermore, the reaction sequences involved allow for the stereocontrolled introduction of functionality at most positions on the triquinane framework and should be capable, therefore, of exploitation in the preparation of many members of the hirsutene class of sesquiterpenoid natural products. Work directed towards such ends is currently underway in our laboratories and results will be reported in due course.

Acknowledgements

We thank the Institute of Advanced Studies and the Australian Research Council for financial support and Dr. Steffen Gross for helpful comments regarding the preparation and use of samarium(II) iodide.

Supplementary data

^1H and ^{13}C NMR spectra for compounds **18** and **19**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.145.

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X-ray crystallographic data for compound **8**: $C_{18}H_{24}O_5$, $M = 320.39$, $T = 200(1)$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 7.9318(2)$, $b = 8.6256(2)$, $c = 24.1464(5)$ Å, $V = 1652.01(7)$ Å^3, $D_x = 1.288$ g cm^{-3}, 2184 unique data ($2\theta_{max} = 55°$), 1560 with $I > 2.0\sigma(I)$; $R = 0.0288$, $R_w = 0.0329$, $S = 1.1475$.
X-ray crystallographic data for compound **11**: $C_{18}H_{26}O_4$, $M = 306.40$, $T = 200(1)$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 7.9337(2)$, $b = 8.5988(2)$, $c = 24.2461(5)$ Å, $V = 1654.08(7)$ Å^3, $D_x = 1.230$ g cm^{-3}, 2185 unique data ($2\theta_{max} = 55°$), 1650 with $I > 2.0\sigma(I)$; $R = 0.0295$, $R_w = 0.0345$, $S = 1.1247$.
X-ray crystallographic data for compound **13**: $C_{22}H_{24}O_5$, $M = 368.43$, $T = 200(1)$ K, trigonal, space group $P3_2$, $Z = 3$, $a = 12.9372(3)$, $b = 12.9372(3)$, $c = 10.0561(2)$ Å, $V = 1457.61(5)$ Å^3, $D_x = 1.259$ g cm^{-3}, 2211 unique data ($2\theta_{max} = 55°$), 1807 with $I > 2.0\sigma(I)$; $R = 0.0316$, $R_w = 0.0343$, $S = 1.0591$.
X-ray crystallographic data for compound **18**: $C_{22}H_{25}NO_6$, $M = 399.44$, $T = 200(1)$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 6.5823(2)$, $b = 7.6057(2)$, $c = 42.1398(11)$ Å, $V = 2109.64(10)$ Å^3, $D_x = 1.258$ g cm^{-3}, 2812 unique data ($2\theta_{max} = 55°$), 1827 with $I > 1.5\sigma(I)$; $R = 0.0333$, $R_w = 0.0384$, $S = 1.1354$.
Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference numbers 613278–613281 for compounds **8**, **11**, **13** and **18**, respectively). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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33. *Selected spectral data for compound* **19**: $[\alpha]_D$ +56 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1H), 3.66 (s, 3H), 2.84–2.63 (complex m, 2H), 2.52 (ddd, $J = 12.3$, 7.5 and 1.5 Hz, 1H), 2.44–2.21 (complex m, 3H), 2.27 (s, 2H), 1.53–1.39 (complex m, 1H), 1.35 (s, 3H), 1.24 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5 (C), 195.0 (C), 178.0 (C), 122.4 (CH), 54.7 (C), 52.5 (CH_2), 52.0 (CH_3), 50.6 (CH), 49.2 (C), 46.3 (CH_2), 44.4 (CH), 37.1 (CH_2), 32.5 (CH_2), 24.5 (CH_3), 24.4 (CH_3); IR ν_{max} (neat)/cm^{-1} 2960, 1728, 1709, 1635, 1467, 1202, 1169, 1093, 876; MS *m*/*z* (EI) 248 ($M^{+\cdot}$, 100%), 233 (32), 189 (75), 188 (70), 173 (63), 120 (70), 108 (92), 91 (55), 81 (68), 80 (82), 79 (68); HRMS found $M^{+\cdot}$, 248.1416; $C_{15}H_{20}O_3$ requires $M^{+\cdot}$, 248.1412. These data match those reported earlier for compound **19**[16b,17] or its racemic modification.[12,15]