An Enantioselective Approach to 3α-Hydroxy-15-rippertene. Construction of the Tetracyclic Ring System

Peter Metz,* Simon Bertels, and Roland Fröhlich

Organisch-Chemisches Institut der Universität Münster, Corrensstrasse 40 D-48149 Münster, Germany

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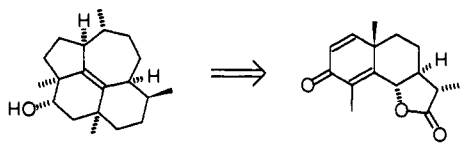
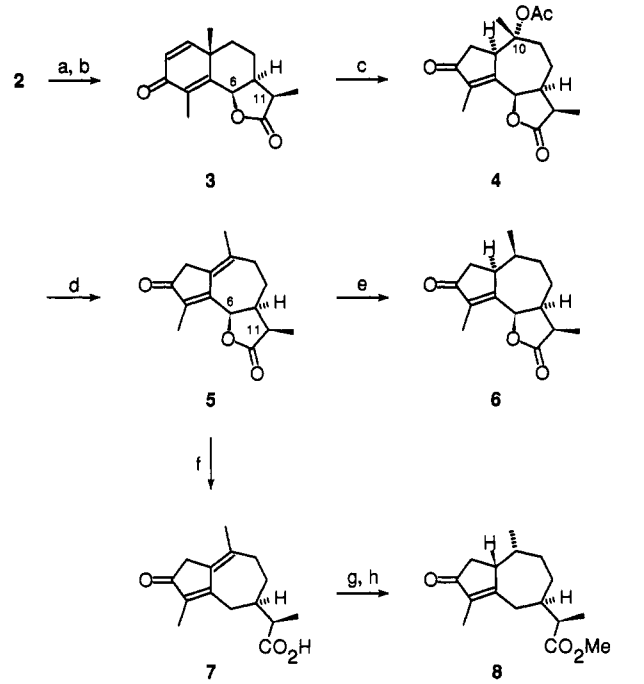
Soldiers of the termite subfamily *Nasutitermitinae* fight predators by ejecting a sticky defense secretion containing structurally unique bi- to tetracyclic diterpenes biosynthetically derived from cembrene A.[1] Recent synthetic endeavors in this area have succeeded in the preparation of two bicyclic secotrinervitanes[2] as well as several naturally occurring[3] or closely related[4] tetracyclic kempanes in racemic form. Here we report an enantioselective route to the ring system of 3α-hydroxy-15-rippertene (**1**),[5] a defense secretion constituent first isolated from *Nasutitermes rippertii*, utilizing the commercially available eudesmanolide (–)-α-santonin (**2**)[6] as the chiral source. Next to a photoisomerization generating the hydroazulene moiety of **1**, an intramolecular vinylogous aldol reaction and an intramolecular Diels–Alder cycloaddition featured key roles in the construction of the tetracyclic olefinic core.



1 **2**

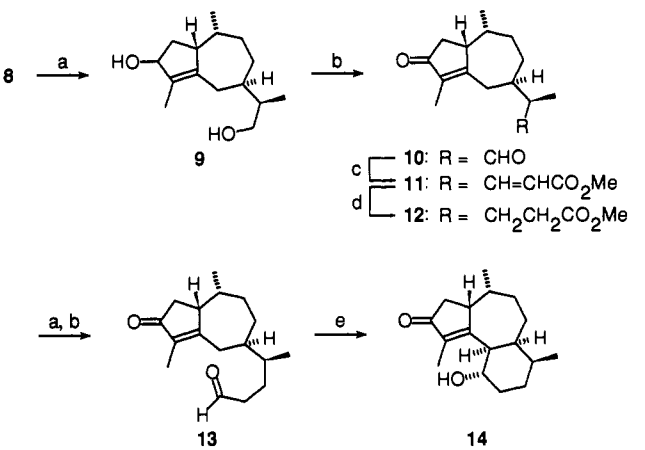
Photolysis[7] of 6-*epi*-β-santonin (**3**),[7a,8] readily obtained from **2** after acid-catalyzed epimerization at C-6[9] and subsequent equilibration at C-11[8] under basic conditions according to modified literature procedures, provided a rapid access to hydroazulene **4**[10] (Scheme I). For stereoselective deoxygenation at C-10, the strategy used by Büchi and co-workers during their synthesis of 1-*epi*-cyclocolorenone[11] was applied. Thus, elimination of acetic acid produced dienone lactone **5**,[7a] which in turn was hydrogenated with complete chemo- and stereoselectivity. But in contrast to the corresponding reaction of the dienone epimeric with **5** at C-6 and C-11,[11] hydrogen added solely from the α-face of **5** to yield

Scheme I[a]



[a] (a) 9% HCl in DMF, 100 °C, 77%. (b) 40 mol % *t*-BuOK, toluene, 20 °C, 69%. (c) *hν*, HOAC, 17 °C, 33%. (d) Concentrated H_2SO_4, 0 °C, 94%. (e) 1 atm H_2, Pd/$BaSO_4$, EtOAC, 20 °C, 73%. (f) $CrCl_2$, HOAc, 2 N HCl, 60 °C, 99%. (g) 1 atm H_2, Pd/C, EtOH, 2 N NaOH, 20 °C. (h) CH_2N_2, ether, MeOH, 0 °C, 72% **8** from **7**.

Scheme II[a]



[a] (a) $LiAlH_4$, ether, 20 °C, 99% from **8**, 98% from **12**. (b) 6 mol % TPAP, NMO, CH_2Cl_2, 20 °C, 90% **10**, 83% **13**. (c) $Ph_3P{=}CHCO_2Me$, toluene, reflux, 76%. (d) 1 atm H_2, Pd/C, EtOAc, 20 °C, 99%. (e) 2% KOH in MeOH, reflux, 69%.

6, as was unambiguously proven by X-ray diffraction analysis. On the other hand, hydrogen addition to acid **7** prepared from **5** *via* hydrogenolysis with chromous chloride occurred, as for its C-11 epimer,[11] predominantly from the β-face (86:14) to give **8** as the major product after esterification and separation by HPLC.[12]

Reduction of keto ester **8** with lithium aluminum hydride afforded diol **9**,[13] which was smoothly oxidized to the keto aldehyde **10** using tetra-*n*-propylammonium perruthenate/*N*-methylmor-

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(2) (a) Kato, T.; Hirukawa, T.; Uyehara, T.; Yamamoto, Y. *Tetrahedron Lett.* **1987**, *28*, 1439–1442. (b) Hirukawa, T.; Koarai, A.; Kato, T. *J. Org. Chem.* **1991**, *56*, 4520–4525. (c) Hirukawa, T.; Shudo, T.; Kato, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 217–225.

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(5) (a) For isolation, elucidation of the relative configuration, and CD studies of **1**, see: Prestwich, G. D.; Spanton, S. G.; Lauher, J. W.; Vrkoč, J. *J. Am. Chem. Soc.* **1980**, *102*, 6825–6828. (b) For assessment of the absolute configuration of **1** by a modified Horeau method, see: Svatoš, A.; Valterová, I.; Fábryová, A.; Vrkoč, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 151–159.

(6) (–)-α-Santonin is available for Sigma, Aldrich, and Fluka.

(7) (a) For photoisomerization of (–)-α-santonin and related compounds, see: Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472–3482. (b) For a recent synthetic application, see: Greene, A. E.; Edgar, M. T. *J. Org. Chem.* **1989**, *54*, 1468–1470.

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(9) Piers, E.; Cheng, K. F. *Can. J. Chem.* **1968**, *46*, 377–383.

(10) Satisfactory spectral and elemental (±0.3% C, H) or HRMS analytical data were obtained for all new compounds.

(11) Büchi, G.; Kauffman, J. M.; Loewenthal, H. J. E. *J. Am. Chem. Soc.* **1966**, *88*, 3403–3408.

(12) Stereochemical assignment for **8** was confirmed by conversion of lactone **6** ($CrCl_2$ and then CH_2N_2, 88% overall) to a stereoisomer identical (capillary GC, ^1H NMR, ^{13}C NMR) to the minor product obtained after hydrogenation and esterification from **7**.

(13) Reduction leads to a single diol stereoisomer with unknown configuration at the endocyclic carbinol center.

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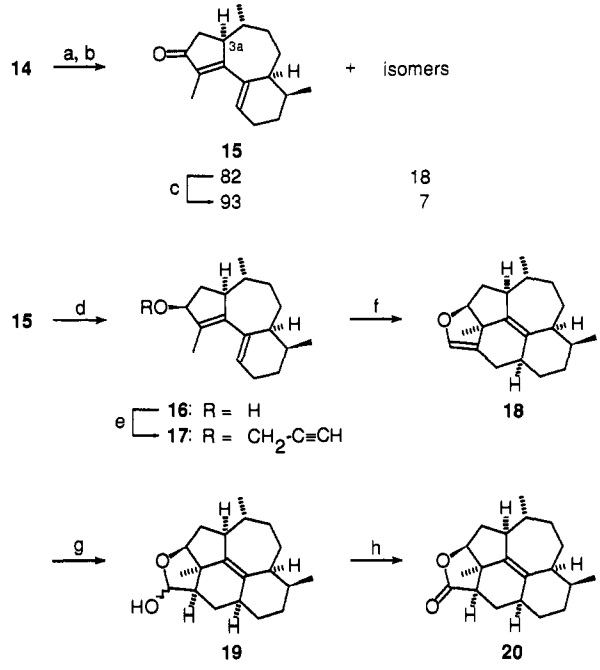
Scheme III[a]



[a] (a) MsCl, Et_3N, CH_2Cl_2, 0 °C. (b) LiBr, DMF, reflux. (c) 10 mol % $RhCl_3 \cdot 3H_2O$, EtOH, reflux, 68% **15** from **14**. (d) $LiAlH_4$, ether, −78 °C to 20 °C, 99%. (e) $HC{\equiv}CCH_2Br$, 20 mol % *n*-Bu_4NI, 50% KOH, 20 °C, 94%. (f) *t*-BuOK, *t*-BuOH, reflux. (g) TsOH, H_2O, THF, *t*-BuOH, 20 °C, 47% **19** from **17**. (h) 3 mol % TPAP, NMO, CH_2Cl_2, 20 °C, 79%.

pholine *N*-oxide[14] (Scheme II). Chain elongation of **10** to **13** was efficiently accomplished by a sequence involving chemoselective Wittig reaction to **11**, chemoselective hydrogenation to **12**, and subsequent adjustment of oxidation levels.[13] Treatment of **13** (2 × 10^{-3} M) with potassium hydroxide in refluxing methanol for 1 h effected a clean and completely stereoselective cyclization to **14**[15] *via* intramolecular vinylogous aldol reaction.[16]

Brief heating of the mesylate derived from **14** with lithium bromide in refluxing DMF[4] provided a mixture of isomeric dienones consisting mainly of **15** (Scheme III). After further enhancement in the relative proportion of this major component by rhodium-catalyzed isomerization of the crude mixture,[4,17] pure **15** was easily isolated by flash chromatography. As anticipated,[18] the elimination step proceeded with concomitant epimerization at C-3a of the primarily formed enone. X-ray diffraction analysis of dienol **16** obtained as a single stereoisomer upon hydride reduction of **15** not only established that this crucial inversion had indeed taken place but also revealed the desired β-orientation of the hydroxyl group. Alkylation of **16** to propargyl ether **17** set the stage for the key intramolecular Diels–Alder reaction. To this end, **17** (3.5 × 10^{-3} M) was treated with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 1–2 h, which effected base-catalyzed isomerization to the corresponding allenyl ether and subsequent [4 + 2] cycloaddition[19] to generate the tetracyclic ring system of 3α-hydroxy-15-rippertene (**1**). Due to the lability of the resultant enol ether **18**, the crude product was directly subjected to acid-catalyzed hydrolysis, furnishing a 7:1 ratio of epimeric lactols **19**. Oxidation[14] of this diastereomeric mixture yielded the homogeneous pentacyclic lactone **20**. Efforts toward introduction of the additional methyl group present in **1** are currently in progress.

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Supplementary Material Available: Crystallographic experimental procedures, solution and refinement of the structures, tables of positional parameters, temperature factors, bond distances, and bond angles, and structure plots for **6** and **16** (12 pages); observed and calculated structure factors (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627. (b) For a review, see: Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19.

(15) The relative configuration of **14** follows from diagnostic $^1H,^1H$ coupling constants and NOE difference data.

(16) For examples of intramolecular vinylogous aldol reactions under basic or acidic conditions, see: (a) Walborsky, H. M.; Reddy, S. M. *J. Org. Chem.* **1988**, *53*, 4851–4852. (b) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.

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(18) Force field calculations (*PCMODEL-PI*, Version 4.0; Serena Software, Bloomington, IN) were performed on **15** and its β(H) epimer at C-3a using starting ring geometries generated by the SCA program (De Clercq, P. J.; Hoflack, J. *Systematic Conformational Analysis*; QCPE Program No. QCMP 079; Indiana University; for a description, see Hoflack, J.; De Clercq, P. J. *Tetrahedron* **1988**, *44*, 6667–6676). Of the minimum energy structures derived, **15** is favored by a 1.9 kcal/mol difference in MMX total energies over its epimer. Significantly, both epimers in their lowest energy conformation ideally fulfil the stereoelectronic requirement for enolization (cf. ref 4) unhampered by steric inaccessibility of the acidic γ-hydrogen.

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