## Enantioselective Synthesis of 4-Desmethyl-3α-hydroxy-15rippertene\*\*

Rabea Hennig and Peter Metz\*

Soldiers of the termite subfamily *Nasutitermitinae* are found worldwide, and they defend themselves against aggressors by ejecting a secretion containing structurally unique tetracyclic diterpenes.<sup>[1]</sup> Synthetically, these unusual natural products have been largely unexplored. So far only the total synthesis of racemic kempene-2 (*rac*-3) is reported,<sup>[2]</sup> whereas a number of other synthetic studies<sup>[3]</sup> have not yet led to the desired kempanes.  $3\alpha$ -Hydroxy-15-rippertene (1) is a tetracyclic diterpene isolated from the defense secretion of termite soldiers from *Nasutitermes rippertii* and *Nasutitermes ephratae* (Scheme 1).<sup>[4]</sup> The compact structure incorporates a sterically



**Scheme 1.** Tetracyclic diterpenes (1, 3) from the defense secretion of higher termites and the retrosynthesis of 1 and 2.

encumbered tetrasubstituted double bond as well as seven stereogenic centers, including two quaternary carbon atoms, representing a challenging synthetic target. Although the biological activity of **1** has not yet been examined, a comparison with antimicrobial trinervitanes<sup>[5]</sup> leads one to assume a similar activity. Several years ago we developed an enantioselective approach to the ring system of **1** from the

[\*] R. Hennig, Prof. Dr. P. Metz Fachrichtung Chemie und Lebensmittelchemie Organische Chemie I, Technische Universität Dresden Bergstrasse 66, 01069 Dresden (Germany) Fax: (+49) 351-463-33162 E-mail: peter.metz@chemie.tu-dresden.de Homepage: http://www.chm.tu-dresden.de/oc1/
[\*\*] We thank Dipl.-Chem. Anne Jäger and Dr. Sebastian Ahrens for the X-ray diffraction analyses, and Takasago Inc. for a generous donation of (-)-isopulegol.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804640.

commercially available sesquiterpene lactone (-)- $\alpha$ -santonin.<sup>[6]</sup> Furthermore, we recently accomplished the enantioselective preparation of the hydroazulene moiety of **1**, commencing with (-)-isopulegol.<sup>[7]</sup>

Herein we report on the first enantioselective synthesis of 4-desmethyl- $3\alpha$ -hydroxy-15-rippertene (2), a close analog of 1, starting from the cyclohexanone 5, which is efficiently made in only four steps from (–)-isopulegol.<sup>[7]</sup> Our synthetic strategy is based on the sequential construction of the ring system in which an intramolecular Diels–Alder reaction<sup>[8]</sup> is the key transformation for the generation of enol ether 4, which features the tetracyclic skeleton as well as five and six correctly installed stereogenic centers of 1 and 2, respectively.

The construction of the first ring was effected by a Lewis acid assisted ring expansion of cyclohexanone **5** to give cycloheptanone **7** using (trimethylsilyl)diazomethane (Scheme 2).<sup>[9]</sup> Despite variation of the Lewis acid used, the two regioisomers **6** and **7** were always obtained as products.<sup>[7]</sup> Cycloheptanone **7** could be converted directly into diketone **8** in excellent yield by using potassium osmate catalyzed dihydroxylation<sup>[10]</sup> of the double bond and subsequent



**Scheme 2.** Synthesis of diketone **8**. a) 1. TMSCHN<sub>2</sub>, Me<sub>3</sub>Al, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \,^{\circ}\text{C} \rightarrow \text{RT}$ , 2. 1 N HCl, THF, RT, 40% **6**, 45% **7**; b) **7**, 5 mol% K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, NalO<sub>4</sub>, pyridine, THF, H<sub>2</sub>O, 0  $^{\circ}\text{C} \rightarrow \text{RT}$ , 93%; c) 1. **6**, LiHMDS, THF,  $-78 \,^{\circ}\text{C}$ , 2. PhCHO,  $-78 \,^{\circ}\text{C}$ , 95%; d) 1. MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0  $^{\circ}\text{C}$ , 2. DBU, CH<sub>2</sub>Cl<sub>2</sub>, RT, 75%; e) LiAlH<sub>4</sub>, Et<sub>2</sub>O,  $-78 \rightarrow 0 \,^{\circ}\text{C}$ , 99%; f) 1. BuLi, THF,  $-78 \,^{\circ}\text{C}$ , 2. ClCO<sub>2</sub>Et,  $-78 \,^{\circ}\text{C}$ , 96%; g) 2 mol% Pd<sub>2</sub>dba<sub>3</sub>, 8 mol% Ph<sub>3</sub>P, HCO<sub>2</sub>H, Et<sub>3</sub>N, THF, 75  $^{\circ}\text{C}$ , 89%; h) 5 mol% OsO<sub>4</sub>, NalO<sub>4</sub>, pyridine, THF, H<sub>2</sub>O, 0  $^{\circ}\text{C} \rightarrow \text{RT}$ , 95%. LiHMDS = lithium hexamethyldisilazide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dba = dibenzylideneacetone.

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



## Communications

glycol cleavage using sodium periodate.<sup>[11]</sup> In contrast, transforming **6** into **8** required an additional 1,2-carbonyl shift,<sup>[12]</sup> which was achieved in six steps with a good overall yield of 57%. An initial aldol condensation of **6** with benzaldehyde (*t*BuOK, *t*BuOH, reflux)<sup>[13]</sup> caused a partial epimerization  $\alpha$  to the carbonyl group, which was avoided by using a sequence consisting of a kinetically controlled deprotonation,<sup>[14]</sup> an aldol reaction with benzaldehyde, and subsequent elimination.<sup>[15]</sup> Removal of the keto functionality from the molecule was accomplished by reduction<sup>[16]</sup> to give the allyl alcohol **9**, esterification to provide the corresponding carbonate **10**,<sup>[17]</sup> and palladium-catalyzed reduction of **10** using triethylamine and formic acid to yield **11**.<sup>[18]</sup> A double osmium tetroxide catalyzed dihydroxylation and subsequent glycol cleavage delivered diketone **8**.<sup>[19]</sup>

An intramolecular aldol condensation of **8** under basic reaction conditions effected ring closure to give the bicyclic product (Scheme 3).<sup>[20]</sup> Annelation of the five-membered ring was accomplished by a short sequence including a diastereo-selective allylation<sup>[21]</sup> to provide **12**, a Wacker oxidation under



Scheme 3. Construction of enol ether 4. a) tBuOK, tBuOH, THF, 65 °C, 81%; b) 1. LiHMDS, THF, 0°C, 2. allyl iodide, 0°C, 84%; c) 5 mol% PdCl<sub>2</sub>, *p*-benzoquinone, DMA, H<sub>2</sub>O, 35 °C, 85%, d) tBuOK, tBuOH, THF, microwaves (150 W), 40 °C, 10 min, 64%; e) LiAlH<sub>4</sub>, Et<sub>2</sub>O,  $-78 \rightarrow$  0 °C, 100%; f) propargyl bromide, 20 mol% TBAI, 50% aq. KOH, toluene, RT, 91%; g) tBuOK, tBuOH, THF, microwave (300 W), 150 °C, 15 min, 83%. DMA = *N*,*N*-dimethylacetamide, TBAI = tetrabutylammonium iodide.

modified conditions,<sup>[22]</sup> and an additional aldol cyclization under microwave irradiation to generate **13**.<sup>[23]</sup> Dienone **13** contained four of the seven stereogenic centers needed for **1** and **2**; the configuration was unambiguously confirmed by X-ray diffraction analysis.<sup>[24]</sup> Construction of the tetracyclic rippertene core was achieved by an efficient intramolecular Diels–Alder reaction from the cyclization precursor **14**, which was made by the diastereoselective reduction of **13** and subsequent etherification using propargyl bromide.<sup>[6]</sup> Compound **14** then underwent isomerization under basic conditions to give the corresponding allenyl ether, which then cyclized under microwave irradiation to yield the enol ether **4** with complete diastereoselectivity.<sup>[25]</sup>

For completion of the norditerpene 2, enol ether 4 was first converted into the lactone 15 by hydration<sup>[26]</sup> and

subsequent TPAP oxidation<sup>[27]</sup> (Scheme 4). An  $\alpha$  hydroxylation with MoOPH,<sup>[28]</sup> basic hydrolysis of the functionalized lactone, and subsequent reduction<sup>[29]</sup> gave a triol; the tetracyclic compound **16** was revealed after oxidative cleav-



Scheme 4. Completion of the synthesis of 2. a) TsOH, THF, H<sub>2</sub>O, RT, 80%; b) 3 mol% TPAP, NMO, MS 4 Å, CH<sub>2</sub>Cl<sub>2</sub>, RT, 100%; c) 1. LiHMDS, THF, -78°C, 2. MoOPH, -78°C, 85%; d) 1. 50% aq. KOH, THF, RT, 2. LiAlH<sub>4</sub>, THF, reflux, 89%; e) NaIO<sub>4</sub>, THF, H<sub>2</sub>O, RT, 98%; f) Me<sub>4</sub>NBH(OAc)<sub>3</sub>, HOAc, MeCN, THF, -20°C, 68%; g) MOMCl, *i*Pr<sub>2</sub>NEt, TBAI, CH<sub>2</sub>Cl<sub>2</sub>, 0°C $\rightarrow$ RT, 57% **18**, 27% **19**; h) 6 N HCl, THF, 50°C, 81%; i) 1. BuLi, THF, 0°C, 2. CS<sub>2</sub>, 0°C, 3. Mel, 0°C, 84%; j) Bu<sub>3</sub>SnH, AIBN, toluene, reflux, 80%; k) 6 N HCl, THF, 50°C, 91%. TsOH = *p*-toluenesulfonic acid, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves, MoOPH = MoO<sub>5</sub>·pyridine·HMPA, MOMCI = methoxymethyl chloride, AIBN = 2,2'-azobis (isobutyronitrile).

age of the 1,2-diol unit. A hydroxy-directed 1,3-*anti* reduction<sup>[30]</sup> afforded diol **17** with high diastereoselectivity; the structure was proven unequivocally by X-ray diffraction analysis.<sup>[24]</sup> Transformation of **17** into the desmethylrippertene **2** required removal of the hydroxy group at C5. To this end, the 3 $\alpha$ -OH group was first protected as the methoxymethyl ether<sup>[31]</sup> (**18**), but a significant quantity of the doubly protected diol **19** was always obtained. However, the protecting groups of **19** could be removed to give **17** in good yield.<sup>[32]</sup> To remove the free 5 $\beta$ -OH group in **18**, it was converted into the corresponding xanthogenate, which was subsequently reduced using tributylstannane and AIBN.<sup>[33]</sup> The final deprotection step to yield the desmethylrippertene **2** proceeded without any problems by using acidic cleavage of the MOM protecting group.<sup>[31]</sup>

The cycloaddition strategy described herein led to the enantioselective synthesis of 4-desmethyl- $3\alpha$ -hydroxy-15-rippertene (2) in only 19 steps from cyclohexanone 5. Installation of the methyl group at C4, which is still missing for the natural product 1, is the subject of ongoing work.

Received: September 21, 2008 Published online: January 7, 2009



Keywords: aldol reaction  $\cdot$  cycloaddition  $\cdot$  diterpenes  $\cdot$  microwave chemistry  $\cdot$  natural products

- a) G. D. Prestwich, *Tetrahedron* 1982, 38, 1911–1919; b) G. D.
   Prestwich, *Sci. Am.* 1983, 249, 78–81, 84–87, 128; c) G. D.
   Prestwich, in *Natural Product Chemistry* (Ed.: Atta-ur-Rahman), Springer, Berlin, 1986, p. 318–329.
- [2] W. G. Dauben, I. Farkas, D. P. Bridon, C.-P. Chuang, K. E. Henegar, J. Am. Chem. Soc. 1991, 113, 5883-5884.
- [3] a) L. A. Paquette, D. R. Sauer, D. G. Cleary, M. A. Kinsella, C. M. Blackwell, L. G. Anderson, J. Am. Chem. Soc. 1992, 114, 7375-7387; b) C. Liu, D. J. Burnell, J. Am. Chem. Soc. 1997, 119, 9584-9585; c) C. Liu, G. Bao, D. J. Burnell, J. Chem. Soc. Perkin Trans. 1 2001, 2644-2656; d) G. Bao, C. Liu, D. J. Burnell, J. Chem. Soc. Perkin Trans. 1 2001, 2657-2668; e) T. Kato, M. Tanaka, S. Takagi, K. Nakanishi, M. Hoshikawa, Helv. Chim. Acta 2004, 87, 197-214; f) B.-C. Hong, F.-L. Chen, S.-H. Chen, J.-H. Liao, G.-H. Lee, Org. Lett. 2005, 7, 557-560; g) G. Bao, L. Zhao, D. J. Burnell, Org. Biomol. Chem. 2005, 3, 3576-3584; h) L. Zhao, D. J. Burnell, Org. Lett. 2006, 8, 155-157; i) F. Caussanel, K. Wang, S. A. Ramachandran, P. Deslongchamps, J. Org. Chem. 2006, 71, 7370-7377.
- [4] G. D. Prestwich, S. G. Spanton, J. W. Lauher, J. Vrkoč, J. Am. Chem. Soc. 1980, 102, 6825–6828.
- [5] C. Zhao, R. W. Rickards, S. C. Trowell, *Tetrahedron* 2004, 60, 10753–10759.
- [6] P. Metz, S. Bertels, R. Fröhlich, J. Am. Chem. Soc. 1993, 115, 12595–12596.
- [7] T. Kreuzer, P. Metz, Eur. J. Org. Chem. 2008, 572-579.
- [8] K. Takao, R. Munakata, K. Tadano, Chem. Rev. 2005, 105, 4779– 4807, and references therein.
- [9] N. Hashimoto, T. Aoyama, T. Shioiri, *Tetrahedron Lett.* 1980, 21, 4619–4622.
- [10] M. Schröder, Chem. Rev. 1980, 80, 187-213.
- T. K. M. Shing, in *Comprehensive Organic Synthesis*, Vol. 7 (Ed.: B. M. Trost), Pergamon, London, **1991**, pp. 703–716.
- [12] V. V. Kane, Tetrahedron 1983, 39, 345-394.
- [13] V. A. Chuiko, Z. V. Vinarskaya, L. V. Izotova, L. Y. Tychinskaya, *Russ. J. Org. Chem.* **2002**, *38*, 196–199.
- [14] P. Zhao, D. B. Collum, J. Am. Chem. Soc. 2003, 125, 4008–4009.
   [15] A. J. Moreno-Vargas, C. Schütz, R. Scopelliti, P. Vogel, J. Org.
- *Chem.* **2003**, *68*, 5632–5640.

- [16] J. Inoue, K. Fukui, T. Kubo, S. Nakazawa, K. Sato, D. Shiomi, Y. Morita, K. Yamamoto, T. Takui, K. Nakasuji, *J. Am. Chem. Soc.* 2001, *123*, 12702–12703.
- [17] Y. J. Lee, K. Lee, S. I. Jung, H. B. Jeon, K. S. Kim, *Tetrahedron* 2005, 61, 1987–2001.
- [18] J. Tsuji, Pure Appl. Chem. 1989, 61, 1673-1680.
- [19] W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, Org. Lett. 2004, 6, 3217– 3219.
- [20] M. Demuth, P. Ritterkamp, E. Weigt, K. Schaffner, J. Am. Chem. Soc. 1986, 108, 4149–4154.
- [21] Y. F. Shealy, C. A. Hosmer, J. M. Riordan, Synthesis 1993, 1095– 1098.
- [22] F. Derdar, J. Martin, C. Martin, J.-M. Brégeault, J. Mercier, J. Organomet. Chem. 1988, 338, C21-C26.
- [23] G. L. Kad, K. P. Kaur, V. Singh, J. Singh, Synth. Commun. 1999, 29, 2583–2586.
- [24] CCDC 691280 (13) and 691281 (17) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.
- [25] a) S. Nagashima, K. Kanematsu, *Tetrahedron: Asymmetry* 1990, 1, 743–749; b) K. Kanematsu, in *Reviews on Heteroatom Chemistry* (Ed.: S. Oae), MYU, Tokyo, 1993, S. 231–259; c) S. Nagashima, T. Taishi, K. Kanematsu, *Heterocycles* 1994, 39, 55–58.
- [26] S. Nagashima, H. Ontsuka, M. Shiro, K. Kanematsu, *Hetero-cycles* 1995, 41, 245-248.
- [27] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, Synthesis 1994, 639–666.
- [28] E. Vedejs, D. A. Engler, J. E. Telschow, J. Org. Chem. 1978, 43, 188–196.
- [29] D. H. Hua, X. Huang, Y. Chen, S. K. Battina, M. Tamura, S. K. Noh, S. I. Koo, I. Namatame, H. Tomoda, E. M. Perchellet, J. P. Perchellet, J. Org. Chem. 2004, 69, 6065-6078.
- [30] a) D. A. Evans, K. T. Chapman, E. M. Carreira, J. Am. Chem. Soc. 1988, 110, 3560-3578; b) T. Hu, N. Takenaka, J. S. Panek, J. Am. Chem. Soc. 2002, 124, 12806-12815.
- [31] G. Stork, T. Takahashi, J. Am. Chem. Soc. 1977, 99, 1275-1276.
- [32] J. Auerbach, S. M. Weinreb, J. Chem. Soc. Chem. Commun. 1974, 298–299.
- [33] P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, L. A. Paquette, J. Am. Chem. Soc. 2001, 123, 9021–9032.