Diterpenes

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

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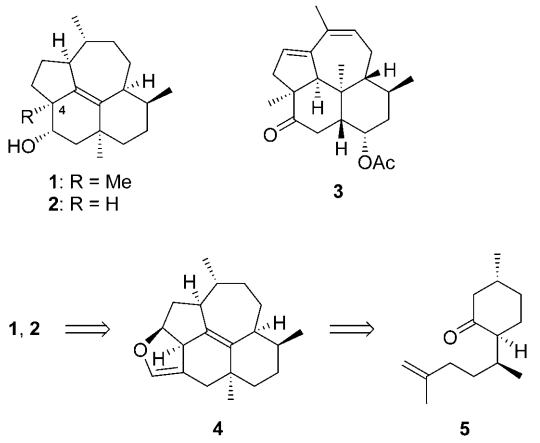
Soldiers of the termite subfamily *Nasutitermitinae* are found worldwide, and they defend themselves against aggressors by ejecting a secretion containing structurally unique tetracyclic diterpenes.[1] Synthetically, these unusual natural products have been largely unexplored. So far only the total synthesis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

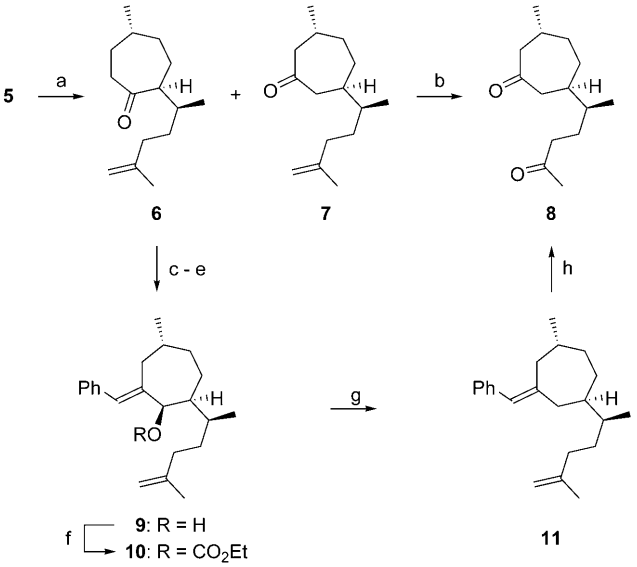


Scheme 1. Tetracyclic diterpenes (**1**, **3**) from the defense secretion of higher termites and the retrosynthesis of **1** and **2**.

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[5] leads one to assume a similar activity. Several years ago we developed an enantioselective approach to the ring system of **1** from the commercially available sesquiterpene lactone (−)-α-santonin.[6] Furthermore, we recently accomplished the enantioselective preparation of the hydroazulene moiety of **1**, commencing with (−)-isopulegol.[7]

Herein we report on the first enantioselective synthesis of 4-desmethyl-3α-hydroxy-15-rippertene (**2**), a close analog of **1**, starting from the cyclohexanone **5**, which is efficiently made in only four steps from (−)-isopulegol.[7] Our synthetic strategy is based on the sequential construction of the ring system in which an intramolecular Diels–Alder reaction[8] 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).[9] Despite variation of the Lewis acid used, the two regioisomers **6** and **7** were always obtained as products.[7] Cycloheptanone **7** could be converted directly into diketone **8** in excellent yield by using potassium osmate catalyzed dihydroxylation[10] of the double bond and subsequent



Scheme 2. Synthesis of diketone **8**. a) 1. $TMSCHN_2$, Me_3Al, CH_2Cl_2, −78 °C→RT, 2. 1 N HCl, THF, RT, 40% **6**, 45% **7**; b) **7**, 5 mol% $K_2OsO_2(OH)_4$, $NaIO_4$, pyridine, THF, H_2O, 0 °C→RT, 93%; c) 1. **6**, LiHMDS, THF, −78 °C, 2. PhCHO, −78 °C, 95%; d) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C, 2. DBU, CH_2Cl_2, RT, 75%; e) $LiAlH_4$, Et_2O, −78→0 °C, 99%; f) 1. BuLi, THF, −78 °C, 2. $ClCO_2Et$, −78 °C, 96%; g) 2 mol% Pd_2dba_3, 8 mol% Ph_3P, HCO_2H, Et_3N, THF, 75 °C, 89%; h) 5 mol% OsO_4, $NaIO_4$, pyridine, THF, H_2O, 0 °C→RT, 95%. LiHMDS = lithium hexamethyldisilazide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dba = dibenzylideneacetone.

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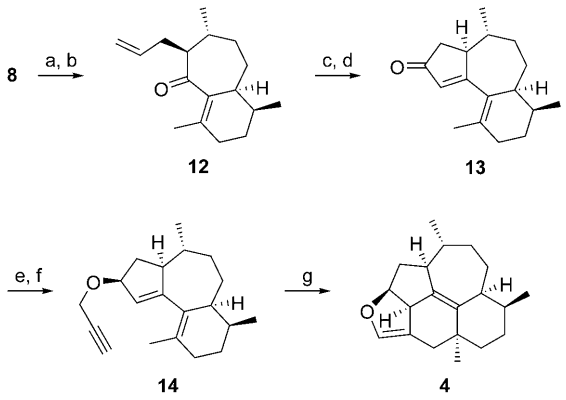
glycol cleavage using sodium periodate.[11] In contrast, transforming **6** into **8** required an additional 1,2-carbonyl shift,[12] which was achieved in six steps with a good overall yield of 57%. An initial aldol condensation of **6** with benzaldehyde (*t*BuOK, *t*BuOH, reflux)[13] caused a partial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

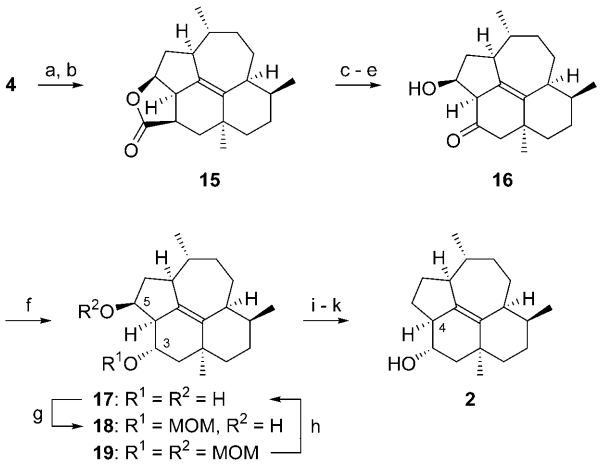
An intramolecular aldol condensation of **8** under basic reaction conditions effected ring closure to give the bicyclic product (Scheme 3).[20] Annelation of the five-membered ring was accomplished by a short sequence including a diastereoselective allylation[21] to provide **12**, a Wacker oxidation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



Scheme 3. Construction of enol ether **4**. a) *t*BuOK, *t*BuOH, THF, 65 °C, 81%; b) 1. LiHMDS, THF, 0 °C, 2. allyl iodide, 0 °C, 84%; c) 5 mol% $PdCl_2$, *p*-benzoquinone, DMA, H_2O, 35 °C, 85%, d) *t*BuOK, *t*BuOH, THF, microwaves (150 W), 40 °C, 10 min, 64%; e) $LiAlH_4$, Et_2O, −78 → 0 °C, 100%; f) propargyl bromide, 20 mol% TBAI, 50% aq. KOH, toluene, RT, 91%; g) *t*BuOK, *t*BuOH, THF, microwave (300 W), 150 °C, 15 min, 83%. DMA = *N*,*N*-dimethylacetamide, TBAI = tetrabutylammonium iodide.

modified conditions,[22] and an additional aldol cyclization under microwave irradiation to generate **13**.[23] Dienone **13** contained four of the seven stereogenic centers needed for **1** and **2**; the configuration was unambiguously confirmed by X-ray diffraction analysis.[24] 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.[6] 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.[25]

For completion of the norditerpene **2**, enol ether **4** was first converted into the lactone **15** by hydration[26] and subsequent TPAP oxidation[27] (Scheme 4). An α hydroxylation with MoOPH,[28] basic hydrolysis of the functionalized lactone, and subsequent reduction[29] gave a triol; the tetracyclic compound **16** was revealed after oxidative cleav-



Scheme 4. Completion of the synthesis of **2**. a) TsOH, THF, H_2O, RT, 80%; b) 3 mol% TPAP, NMO, MS 4 Å, CH_2Cl_2, RT, 100%; c) 1. LiHMDS, THF, −78 °C, 2. MoOPH, −78 °C, 85%; d) 1. 50% aq. KOH, THF, RT, 2. $LiAlH_4$, THF, reflux, 89%; e) $NaIO_4$, THF, H_2O, RT, 98%; f) $Me_4NBH(OAc)_3$, HOAc, MeCN, THF, −20 °C, 68%; g) MOMCl, iPr_2NEt, TBAI, CH_2Cl_2, 0 °C → RT, 57% **18**, 27% **19**; h) 6 N HCl, THF, 50 °C, 81%; i) 1. BuLi, THF, 0 °C, 2. CS_2, 0 °C, 3. MeI, 0 °C, 84%; j) Bu_3SnH, 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_5·pyridine·HMPA, MOMCl = methoxymethyl chloride, AIBN = 2,2′-azobis(isobutyronitrile).

age of the 1,2-diol unit. A hydroxy-directed 1,3-*anti* reduction[30] afforded diol **17** with high diastereoselectivity; the structure was proven unequivocally by X-ray diffraction analysis.[24] Transformation of **17** into the desmethylrippertene **2** required removal of the hydroxy group at C5. To this end, the 3α-OH group was first protected as the methoxymethyl ether[31] (**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.[32] To remove the free 5β-OH group in **18**, it was converted into the corresponding xanthogenate, which was subsequently reduced using tributylstannane and AIBN.[33] The final deprotection step to yield the desmethylrippertene **2** proceeded without any problems by using acidic cleavage of the MOM protecting group.[31]

The cycloaddition strategy described herein led to the enantioselective synthesis of 4-desmethyl-3α-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.

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