Diterpenes

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Enantioselective Total Synthesis of the Diterpenes Kempene-2, Kempene-1, and 3-*epi*-Kempene-1 from the Defense Secretion of Higher Termites**

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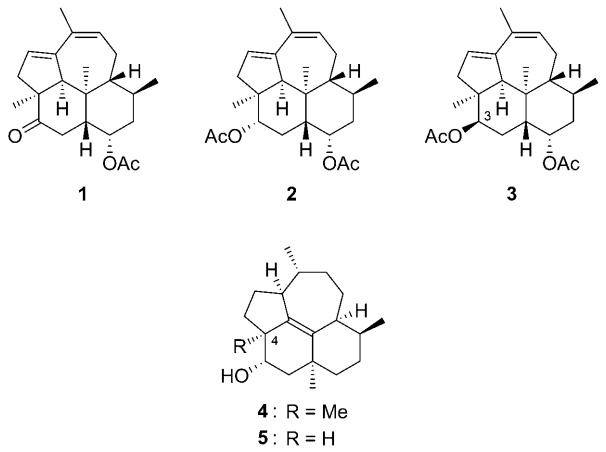
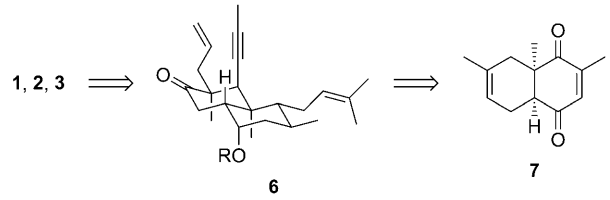
Dedicated to Professor Jochen Mattay on the occasion of his 65th birthday

Soldiers of the termite subfamily *Nasutitermitinae* found worldwide defend themselves against aggressors by ejecting a secretion containing structurally unique tetracyclic diterpenes.[1] Kempene-2 (**1**), kempene-1 (**2**), and 3-*epi*-kempene-1 (**3**) are diterpenes with a kempane skeleton isolated first from the defense secretion of termite soldiers of the species *Nasutitermes kempae*[2] and *Bulbitermes singaporensis*[3] (Scheme 1).[4,5] The synthesis of these exceptional natural products has proven to be problematic. So far, only the total synthesis of racemic kempene-2 (*rac*-**1**) has been reported,[6] whereas a number of other synthetic studies[7] have not yet led to the desired kempanes. Recently, we achieved the enantioselective synthesis of 4-desmethyl-3α-hydroxy-15-rippertene (**5**), a close analogue of rippertene **4**, which was isolated from *Nasutitermes rippertii* and *Nasutitermes ephratae*; an intramolecular Diels–Alder reaction was the key transformation in the synthesis.[8] Recent studies[9] on the biological activity of **5** showed that this norditerpene exhibits an antibiotic activity against *B. subtilis* similar to that of antimicrobial trinervitanes.[10] In the course of our work[11] on the construction of hydroazulenes through domino metathesis reactions[12,13] we have now selected the tetracyclic kempanes **1**–**3** as challenging synthetic targets with seven and eight contiguous stereogenic centers, respectively, including two quarternary carbon atoms.



Scheme 1. Tetracyclic diterpenes (**1**–**4**) from the defense secretion of higher termites and the synthetic analogue **5**.

Herein we report on the first enantioselective synthesis of the diterpenes **1**–**3** by the domino metathesis reaction of a suitably substituted dienyne **6**, which in turn was obtained from the bicyclic compound **7** generated in high enantiomeric purity by a catalytic asymmetric Diels–Alder reaction (Scheme 2).[14,15]



Scheme 2. Retrosynthesis of kempanes **1**–**3**.

For the enantioselective synthesis of dienyne **6** an asymmetric [4+2] cycloaddition of 2,6-dimethyl-1,4-benzoquinone (**8**) with isoprene (**9**) was used, which was catalyzed very efficiently by the oxazaborolidine aluminum tribromide complex **10** (Scheme 3).[14,15] Under optimized reaction conditions **7** was obtained in very good yield and with excellent regioselectivity (> 99:1) and high enantiomeric excess on a gram scale. This reaction constitutes a formal enantioselective synthesis of kempene-2 (**1**), since *rac*-**7** was already transformed to *rac*-**1**. However, in contrast to the present work, a McMurry reaction served as the key step to generate the seven-membered ring of the target molecule in moderate yield.[6] After reduction of the electron-deficient olefin in **7** under equilibrating conditions,[6] the pure stereoisomer **11** was isolated in 31% yield. Three additional diastereomers of **11** were isolated (68% overall yield) and could partially be converted to **11** by treating again with zinc and acetic acid. A chemo- and diastereoselective reduction of diketone **11** with L-selectride delivered alcohol **12**,[6] which was converted to

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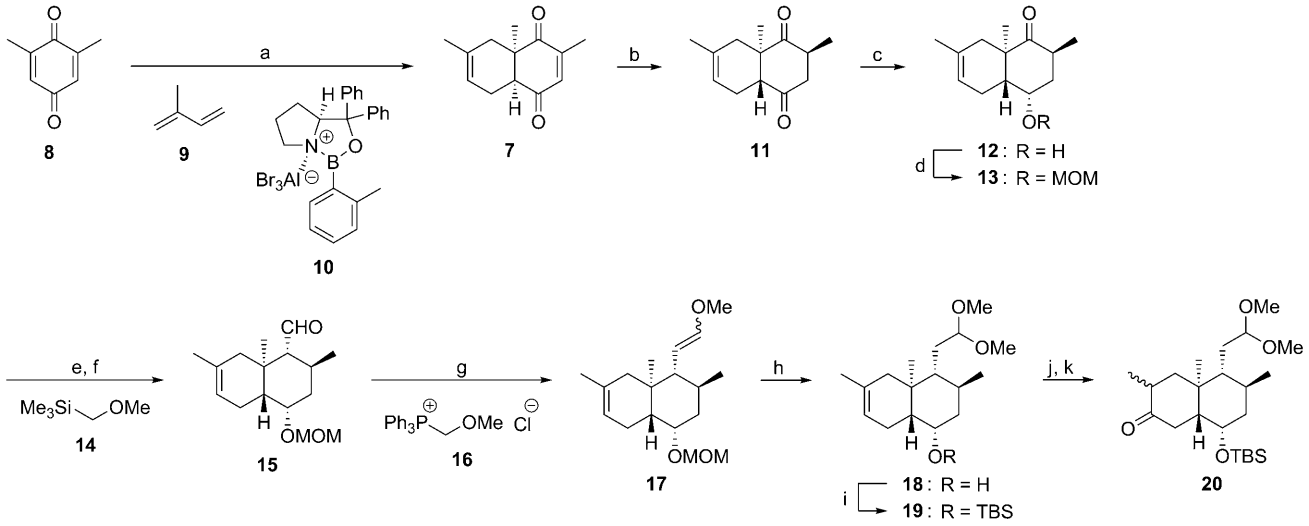
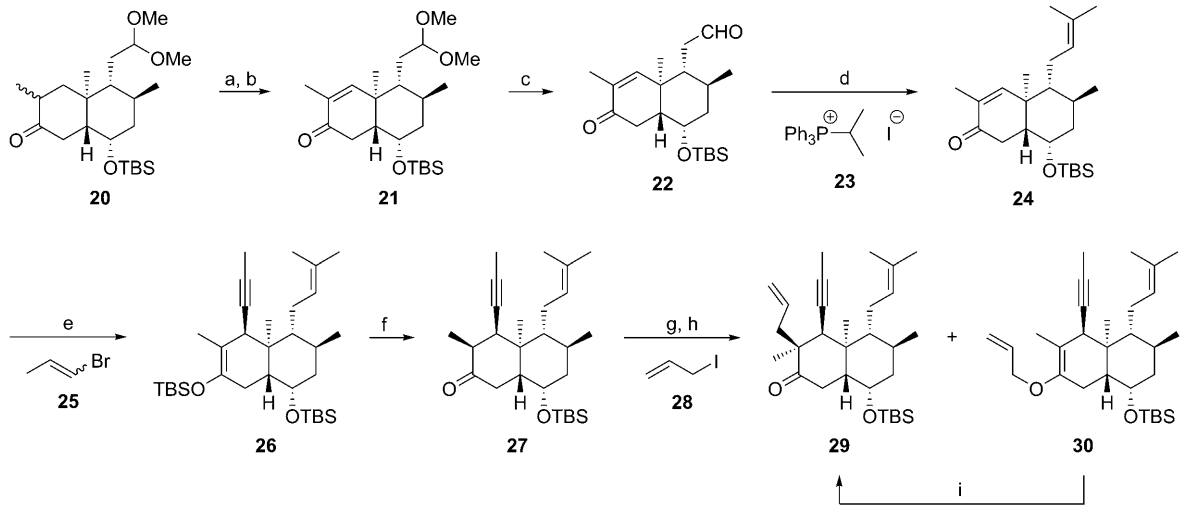


Scheme 3. Catalytic enantioselective Diels–Alder route to bicyclic ketone **20**. a) **9**, 5 mol% **10**, CH_2Cl_2, −78 °C, 98%, 94% *ee*; b) Zn, HOAc, reflux, 31% **11** (+68% diastereomers); c) L-selectride, THF, −78 °C, 90%; d) MOMCl, *i*Pr_2NEt, CH_2Cl_2, reflux, 96%; e) 1. **14**, sBuLi, THF, −60→−23 °C, 2. **13**, −78→−60 °C, 3. KH, −60 °C→RT; f) TFA, CH_2Cl_2, RT, 65% (2 steps; 79% based on recovered **13**); g) 1. **16**, LiHMDS, THF, 0 °C, 2. **15**, 0 °C, 87%; h) TsOH, MeOH, reflux, 87%; i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; j) BH_3·SMe_2, THF, 0 °C, 83%; k) DMP, CH_2Cl_2, 0 °C→RT, 91%. DMP = Dess–Martin periodinane, L-selectride = lithium tri-*sec*-butylborohydride, LiHMDS = lithium hexamethyldisilazide, MOMCl = methoxymethyl chloride, TBSOTf = *tert*-butyldimethylsilyl triflate, TFA = trifluoroacetic acid, TsOH = toluenesulfonic acid.

the MOM ether **13**. In analogy to the Dauben route,[6] an efficient chain extension of **13** to give aldehyde **15** succeeded by application of silane **14** in a Peterson olefination followed by acidic hydrolysis. Another carbonyl olefination of **15** with the ylide derived from **16** led to enol ether **17**. Treatment of **17** with methanol and acid effected both solvolysis of the MOM ether and formation of a dimethyl acetal to afford **18**. After silylation to give **19**, ketone **20** was obtained by hydroboration/oxidation and subsequent Dess–Martin oxidation as a mixture of two diastereomers.

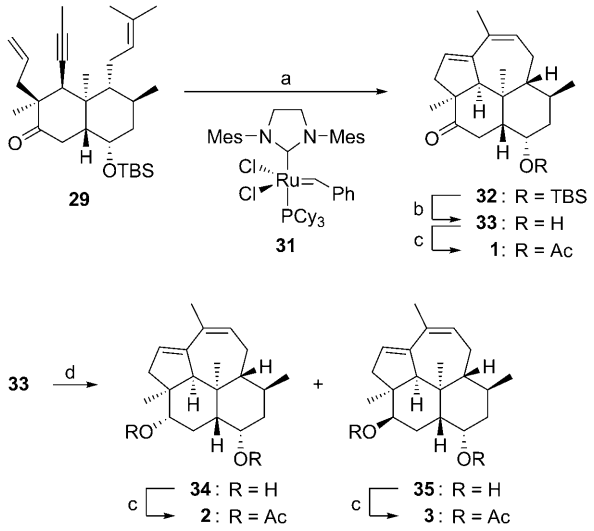
Generation of the trimethylsilyl enol ether of **20** under thermodynamic control[16] and oxidation with DDQ[7a] led to enone **21**. Cleavage of the dimethyl acetal under mild conditions[17] gave aldehyde **22** (Scheme 4). Chemoselective Wittig reaction of **22** with the ylide derived from **23** then yielded the bicyclic enone **24**. Conjugate addition of the propynyl aluminate[18,19] generated from **25** led to silyl enol ether **26** as a single diastereomer, and after mild hydrolysis ketone **27** was isolated. A completely diastereoselective[20] α-allylation of **27** to give the desired dienyne **29** (**6** with R =



Scheme 4. Conversion of bicyclic ketone **20** into dienyne **29**. a) TMSI, HMDS, THF, RT; b) DDQ, benzene, RT, 67% (2 steps); c) PPTS, acetone, reflux, 97%; d) 1. **23**, BuLi, THF, 0 °C, 2. **22**, 0 °C, 90%; e) 1. **25**, BuLi, THF, −78 °C, 2. Me_3Al, −78 °C, 3. **24**, TBSOTf, −78 °C, 84%; f) 2 N HCl, THF, RT, 97%; g) TMSI, HMDS, THF, RT; h) 1. MeLi, 0 °C, 2. **28**, HMPA, −20 °C, 40% **29** + 52% **30** (2 steps); i) toluene, reflux, 90%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, HMDS = hexamethyldisilazane, HMPA = hexamethylphosphoramide, PPTS = pyridinium *p*-toluenesulfonate, TMSI = trimethylsilyl iodide.

TBS) succeeded by reaction of the lithium enolate formed under thermodynamic control with **28**. Allyl ether **30** also generated in this reaction could be converted with complete diastereoselectivity to **29** by means of a Claisen rearrangement.

Completion of the synthesis of kempenes **1**–**3** was initiated by the domino metathesis reaction[11–13] of dienyne **29** using the Grubbs II catalyst **31** (Scheme 5). This reaction furnished



Scheme 5. Domino metathesis of **29** and completion of the synthesis of kempene-2 (**1**), kempene-1 (**2**), and 3-*epi*-kempene-1 (**3**). a) 5 mol% **31**, CH_2Cl_2, reflux, 92%; b) Bu_4NF, THF, reflux, 100%; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, 91% **1**, 100% **2**, 100% **3**; d) $LiAlH_4$, THF, 0°C, 60% **34** + 26% **35**. Cy = cyclohexyl, DMAP = 4-dimethylaminopyridine, Mes = mesityl.

the protected tetracyclic compound **32** with high efficiency as the only cyclization product. This key step could also be realized in good yield (82%) with 10 mol% of the Grubbs I catalyst. Silyl ether **32** was quantitatively deprotected to afford alcohol **33**, which finally gave (+)-kempene-2 (**1**) after acetylation. A circular dichroism (CD) spectrum (MeOH) of synthetic **1** exhibited a strong positive Cotton effect at 294 nm ($\Delta\varepsilon = +1.43$) as was reported for the natural product **1** (289 nm, $\Delta\varepsilon = +1.46$).[2,21] This confirms the absolute configuration assigned by Prestwich, since the stereochemical control by catalyst **10** is well understood.[14,15] Reduction of **33** with lithium aluminum hydride led to a 2.3:1 mixture of diols **34** and **35**.[3] Acetylation of these diols to give (+)-kempene-1 (**2**) and (+)-3-*epi*-kempene-2 (**3**) proceeded very efficiently.[3]

In summary, we have accomplished the enantioselective total synthesis of (+)-kempene-2 (**1**) commencing with 2,6-dimethyl-1,4-benzoquinone (**8**) in only 23 steps with an overall yield of 3.2%. The diterpenes (+)-kempene-1 (**2**) and (+)-3-*epi*-kempene-1 (**3**) were obtained in 24 steps each. Owing to the domino metathesis strategy, the efficiency of the route developed here is considerably higher than that of the reported synthesis of *rac*-**1**[6] and can be increased further by recycling of the undesired diastereomers of **11**.

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