Synthetic Studies toward the Kempane Diterpenes: Preparation of the Ring System

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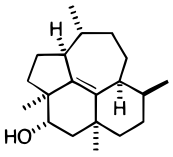
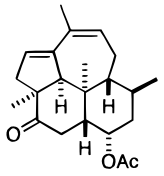
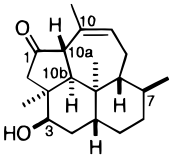
The defensive secretions of nasute soldier termites include tetracyclic diterpenes of two closely related types, the rippertanes (e.g., **1**) and the kempanes (e.g., **2** and **3**).[1] We report herein an approach to the synthesis of the ring system of the kempane diterpenes in a manner that should allow access to all of the known kempanes from one multifunctional pentacyclic compound. Previous approaches to the kempanes have led to only one total synthesis. The Dauben group[2] prepared kempene-2 (**2**) by a clever route in which, at different points in the synthesis, two rings were established by Diels−Alder additions of isoprene. Paquette and co-workers[3] reported an approach to kempane **3** that included a remarkably efficient palladium-catalyzed [3 + 2] cycloaddition. An isomer of **3** was prepared in which the double bond was conjugated with the ketone, but, unfortunately, they were unable to transform this isomer into the less-stable[4] natural product. In the only enantioselective approach, Metz *et al.*[5] assembled a *nor*-methyl skeleton for 3α-hydroxy-15-rippertene (**1**) from (−)-α-santonin.



1



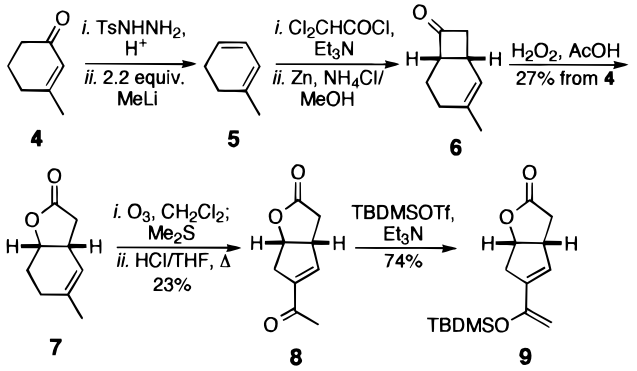
2



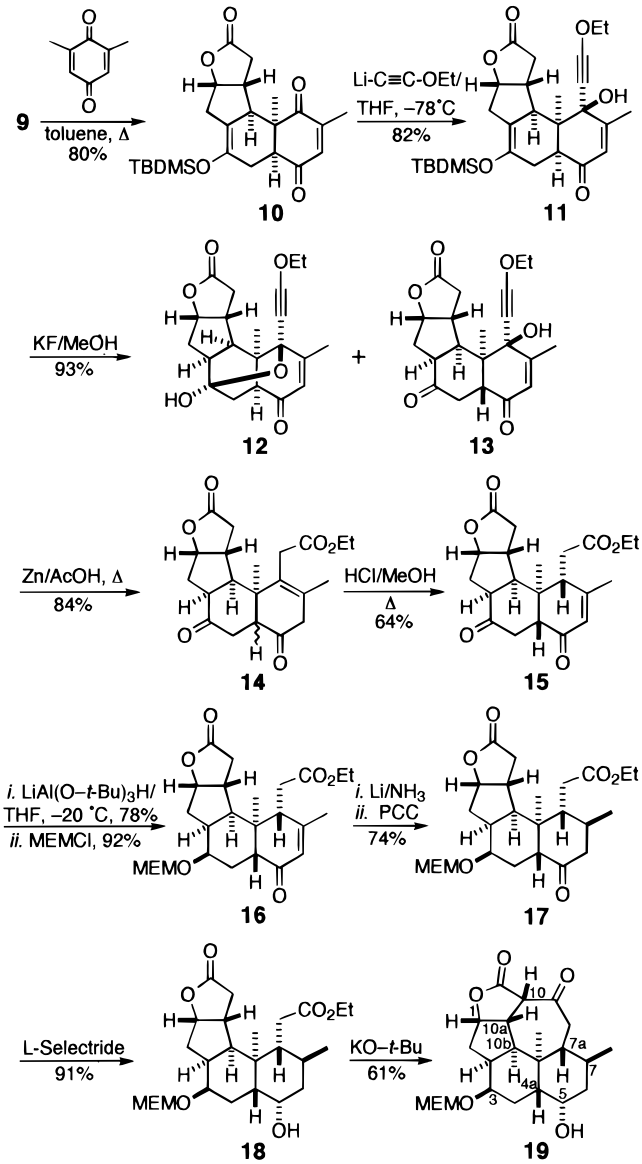
3

Our strategy was to use a Diels−Alder reaction to establish the relative stereochemistry for the central stereogenic centers at C-10a, C-10b, and C-10c.[6] The diene was required to have oxygens at the same locations as in **2** and/or **3**, and functionality should already be present that would be needed for the closure of the final, seven-membered ring. An appropriate diene (**9**) was constructed from enone **4** by a route reminiscent of Corey's work,[7,8] as outlined in Scheme 1. The trapping of dichloroketene by diene **5** proceeded regiospecifically,[9] as did a subsequent Baeyer−Villiger reaction (**6** → **7**). Ring scission of **7** and acid-mediated aldol gave enone **8**, which was most efficiently converted to the silyl enol ether **9** using the triflate and triethylamine.[10]

Scheme 1



Scheme 2



(1) (a) Baker, R.; Walmsley, S. *Tetrahedron* **1982**, *38*, 1899−1910. (b) Prestwich, G. D. *Tetrahedron* **1982**, *38*, 1911−1919.

(2) Dauben, W. G.; Farkas, I.; Bridon, D. P.; Chuang, C.-P.; Henegar, K. E. *J. Am. Chem. Soc.* **1991**, *113*, 5883−5884.

(3) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375−7387.

(4) Taber, D. F. *Tetrahedron Lett.* **1993**, *34*, 1883−1884.

(5) Metz, P.; Bertels, S.; Fröhlich, R. *J. Am. Chem. Soc.* **1993**, *115*, 12595−12596.

(6) The numbering of kempane **3** is used for all of the compounds shown in Scheme 2.

(7) For instance, see: Corey, E. J.; Ravindranathan, T. *Tetrahedron Lett.* **1971**, 4753−4755.

(8) A lactone very similar to **7** has been resolved with (+)-1-(1-naphthyl)ethylamine: Corey, E. J.; Snider, B. B. *J. Org. Chem.* **1974**, *39*, 256−258.

(9) Chemo- and regiospecific trapping of ketene with a 1-substituted 1,3-cyclohexadiene can also be seen in: Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988**, *53*, 4877−4883.

(10) (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953−5956. (b) Ihara, M.; Ishida, Y.; Fukumoto, K.; Kametani, T. *Chem. Pharm. Bull.* **1985**, *33*, 4102−4105.

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As shown in Scheme 2,[6] the Diels−Alder reaction of **9** with 2,6-dimethyl-1,4-benzoquinone proceeded smoothly in a regio-, stereo-, and facially-selective manner to provide adduct **10**, in which three of the four rings of the kempanes were already in place. An examination of the relative accessibilities[11] of the two ketones in **10** to axial attack led to the correct prediction of addition of ethoxyacetylide to provide **11** exclusively. Release of the silyl group with fluoride ion gave **12** and **13** in a 7:1 ratio, respectively. Formation of the hemiacetal **12** confirmed the relative stereochemistry at the carbinol center in **11**. NOE measurements established that the minor product **13** had epimerized at C-4a. Reduction and solvolysis of the mixture of **12** and **13** was carried out in a single operation with zinc in refluxing acetic acid. This yielded the β,γ-unsaturated ketone **14**, which included a minor component that was epimeric at C-4a (6:1 *cis* to *trans* ratio). Treatment of **14** with HCl in methanol completed the epimerization process, and the double bond was brought into conjugation concomitantly providing only one enone, **15**. NOE measurements established that the methyl at C-10c and C-4aH were now *trans* and that C-4aH and C-7aH were *cis*, i.e., the ester chain had assumed the required, thermodynamically-preferred equatorial position. Reduction of **15** with $NaBH_4$ in 1:1 $MeOH/CH_2Cl_2$ at −78 °C[12] was completely chemoselective but not stereoselective. A 1.5:1 mixture, epimeric at C-3, was obtained, undesired equatorial alcohol was the major component. On the other hand, only the ketone at C-3 was reduced, predominantly by equatorial addition of hydride, with $LiAl(O\text{-}t\text{-}Bu)_3H$,[13] and the axial alcohol was protected with (2-methoxyethoxy)methyl chloride to give **16**. The equatorial position for the C-7 methyl in **17** developed as a result of the dissolving-metal reduction of the enone in **16**. Reduction of the remaining ketone by equatorial attack with L-Selectride provided **18**. Dieckmann cyclization of the final seven-membered ring with KO-*t*-Bu afforded the pentacyclic target **19**, which has all of the stereogenic centers of the kempane diterpenes in their correct configurations (once again confirmed by NOE measurements) and oxygen functionality on every ring. The oxygen functions at C-1, C-3, and C-5 are as found in various kempanes; the lactone can be reduced to a C-10 methyl or may be used to facilitate methylation; and a remaining methyl group (at C-2a) can be introduced by 1,4-addition to an α,β-unsaturated C-1 ketone. Modification of **19** to **2** and **3** is currently underway in our laboratory.

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Supporting Information Available: Procedures for the preparation of compounds **10**−**19** and ^1H and ^{13}C NMR spectra of **10**−**19** (31 pages). See any current masthead page for ordering and Internet access instructions.

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(11) (a) Liotta, D.; Saindane, M.; Sunay, U.; Jamison, W. C. L.; Grossman, J.; Phillips, P. *J. Org. Chem.* **1985**, *50*, 3243−3245. (b) Liu, C.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 3683−3687.

(12) Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517−520.

(13) $LiAl(O\text{-}t\text{-}Bu)_3H$ provided the axial alcohol and its C-3 epimer in a 8:1 ratio and in a combined yield of 88%. The epimers were separable by flash chromatography. The relative stereochemistry at the carbinol center was assigned on the basis of NOE measurements.