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A 4 + 3 Cycloaddition Approach to the Synthesis of Spatol. A Formal Total Synthesis of Racemic Spatol

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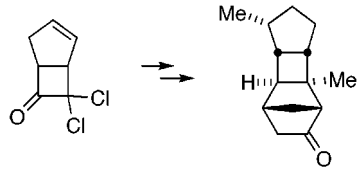
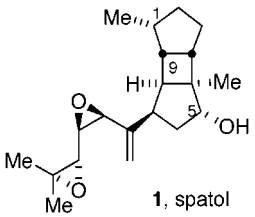
ABSTRACT

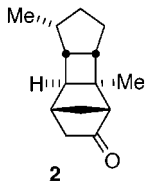


A formal total synthesis of racemic spatol is presented. The key steps involved a 4 + 3 cycloaddition of a halogenated cyclopentenyl cation to cyclopentadiene and a quasi-Favorskii rearrangement.

The diterpene spatol (**1**) was isolated from the brown algae *Spatoglossum howleii*.[1] It is of interest not only because of its relatively unique structure but also its biological activity. It has been shown to possess an ED_{50} of 1.2 μg/mL against fertilized sea urchin eggs (*Lytechinus pictus*). It was also active against human T242 melanoma and 224C astrocytoma cell lines in vitro with activity ranging from 1 to 5 μg/mL.



1, spatol



2

A number of synthetic studies directed toward spatol and other spatane diterpenes have appeared.[2] The synthetic challenges include the stereoselective preparation of the *cis*,*anti*,*cis*-tricyclo[5.3.0.$0^{2,6}$]decane skeleton as well as the labile diepoxide functionality. Of the known syntheses to spatol, one which particularly attracted our attention was the elegant approach of Salomon and co-workers.[2a,h] In the course of their work, they produced the intermediate **2**, which was carried on to spatol.

In an effort to more fully explore and exploit the 4 + 3 cycloaddition reaction chemistry of cyclic, halogenated oxyallylic cations,[3] we decided to pursue a formal synthesis of **1** via a synthesis of **2**.

The key steps in the synthesis were to be the generation of the oxyallylic cation **4** from **3** and the cycloaddition of the former to cyclopentadiene to afford **5**. This would be followed by a quasi-Favorskii rearrangement to produce the cyclobutyl carboxaldehyde **6** (Scheme 1). Though we had

(1) (a) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233−41. (b) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 3325−9.

(2) Approaches to the spatane system: (a) Salomon, R. G.; Sachinvala, N. D.; Roy, S.; Basu, B.; Raychaudhuri, S. R.; Miller, D. B.; Sharma, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 3085−95. (b) Miesch, M.; Cotte, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1993**, *34*, 8085−6. (c) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379−1389. Total syntheses of spatanes: (d) Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211−13. (e) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3035−8. (f) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 6109−12. (g) Dauben, W. G.; Kowalczyk, B. A. *Tetrahedron Lett.* **1990**, *31*, 635−8. (h) Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096−106. (i) Miesch, M.; Cotté, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1994**, *35*, 7021−2. (j) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1994**, *50*, 12829−42.

(3) (a) Harmata, M.; Shao, L.; Kurti, L.; Abeywardane, A. *Tetrahedron Lett.* **1999**, *40*, 1075−1078. (b) Harmata, M.; Shao, L. *Synthesis* **1999**, 1534−1540.

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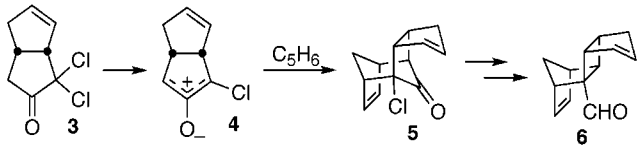
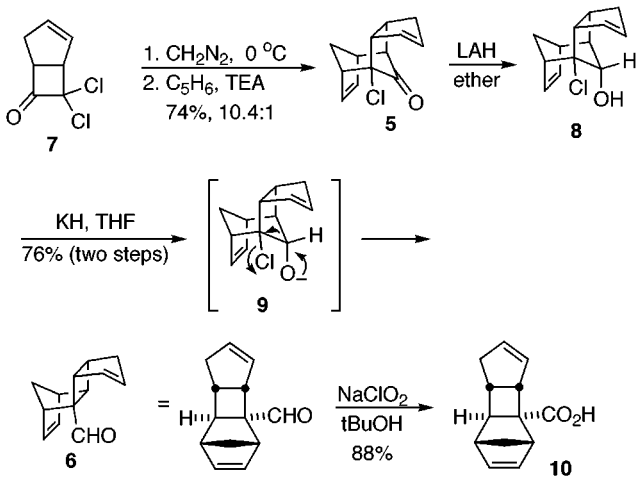
Scheme 1



already demonstrated the feasibility of this approach by using a simple model system,[4] the key steps in the process were worth exploring, since the number of examples of quasi-Favorskii rearrangements of α-chloroketones is still small. Furthermore, our intention to pursue a formal total synthesis demanded a much more comprehensive approach to the problem than had previously been undertaken.

We began our work with the commercially available dichlorocyclobutanone **7**. As shown in Scheme 2, ring ex-

Scheme 2



pansion with diazomethane gave the corresponding cyclopentanone **3**. Because it decomposed relatively rapidly, ketone **3** was immediately reacted with cyclopentadiene and triethylamine in a 1:1 mixture of trifluoroethanol and ether to afford the 4 + 3 cycloaddition adduct **5** as a 10.4:1 mixture of endo/exo isomers in 74% yield.[5] The structural assignments were made on the basis of the chemical shift difference between the olefinic protons in the two isomers. In the endo isomer, the olefinic protons (6.28−6.23 ppm) are in the shielding cone of the carbonyl group and thus appear upfield of those in the exo isomer (6.65−6.56 ppm).

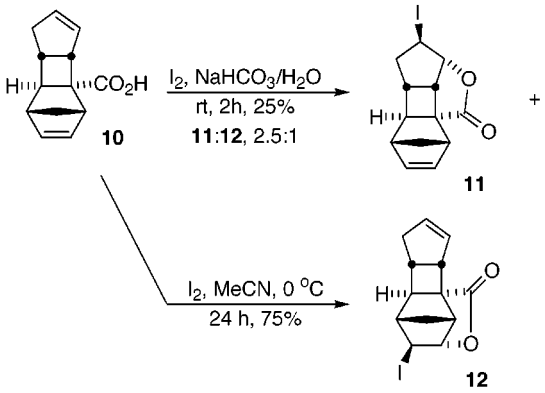
Reduction of **5** with lithium aluminum hydride gave the alcohol **8**. The stereochemical assignment of the carbinol carbon was based on precedent.[4] Treatment of **8** with potassium hydride in THF afforded the aldehyde **6** in 76% yield, presumably through the intermediate **9**. The aldehyde

(4) Harmata, M.; Rashatasakhon, P. *Tetrahedron Lett.* **2001**, *42*, 0000.
(5) The isomer ratio was determined by ^{1}H NMR of the crude reaction mixture.

was oxidized to the carboxylic acid **10** in 88% yield using sodium chlorite.[6]

Iodolactonization of this acid proved interesting (Scheme 3).[7] Under kinetically controlled conditions (I_2, $NaHCO_3$/

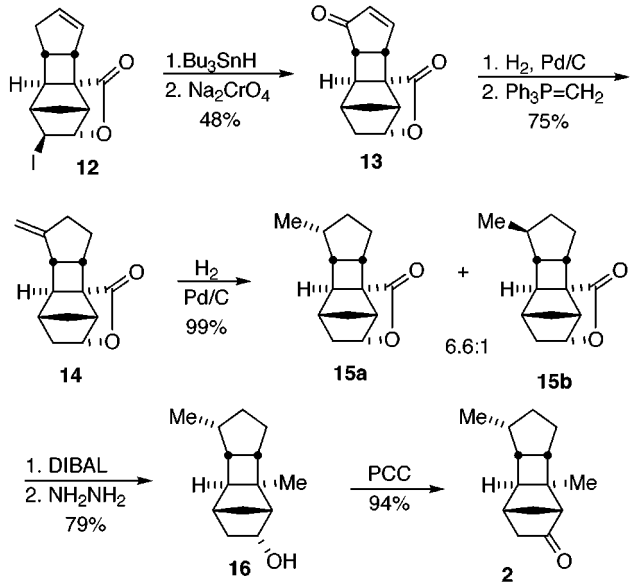
Scheme 3



H_2O, rt, 2 h), two regioisomers, **11** and **12**, were obtained in a ratio of 2.5:1 in favor of **11**. Semiempirical calculations (AM1)[8] suggested that in fact **12** was thermodynamically more stable, and indeed, when the reaction was run under conditions of thermodynamic control, **12** was produced as the sole product in 75% yield.

Processing of **12** included radical dehalogenation[9] and allylic oxidation with sodium chromate[10] to afford the enone **13** in 48% yield (Scheme 4). The relative stereochemistry

Scheme 4



of the system was rigorously defined at this point by an X-ray analysis of a single crystal of **13**. Hydrogenation of **13** and Wittig olefination produced the exocyclic alkene **14** in a good overall yield of 75%.

We next wanted to set the stereochemistry of position 1 (spatol numbering) via hydrogenation, as others had done.[2] In the best possible case, the isomers **15a** and **15b** were obtained in virtually quantitative yield in a ratio of 6.6:1 using a 10% palladium on carbon catalyst in ethyl acetate under H_2 at 145 psi. These isomers were not separable, at least by flash chromatography, and we did our subsequent work on the mixture. Reduction of the lactone in **15** with DIBAL followed by a Wolff−Kishner reaction afforded compound **16** in 79% yield. Simple PCC oxidation produced ketone **2**. The major diastereomer was isolated by low-temperature recrystallization, the procedure reported by Salomon.[2a] The proton and carbon NMR data for ketone **2** matched those reported in the literature.[2d]

In conclusion, we have demonstrated an application of the 4 + 3 cycloaddition reaction of a halogenated, cyclopentenyl oxyallylic cation and the subsequent quasi-Favorskii rearrangement. It offers a unique, nonphotochemical[2b,i] method for producing cyclobutanes. The entire process proceeds in 9.8% overall yield over 14 steps from commercially available starting material. We plan to attempt an asymmetric synthesis of spatol using similar chemistry. Details will be reported in due course.

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Supporting Information Available: Experimental procedures, spectra for all intermediates, and X-ray data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Gonzalez, F. B.; Bartlett, P. A. *Org. Synth*. **1986**, *64*, 175−81.
(8) ΔH_f(**11**) = −1.84 kcal/mol; ΔH_f(**12**) = −5.33 kcal/mol.
(9) Kuivila, H. G. *Synthesis* **1970**, 499−509.
(10) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc*. **1984**, *106*, 6690−6693.