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Intramolecular 4 + 3 Cycloadditions. Aspects of Stereocontrol in the Synthesis of Cyclooctanoids. A Synthesis of (+)-Dactylol†

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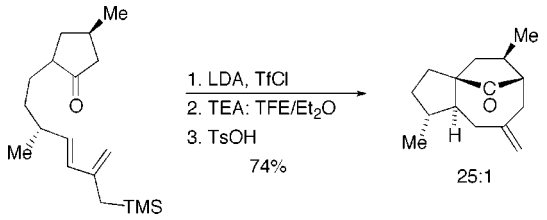
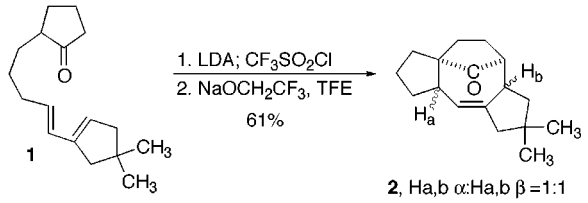
ABSTRACT



The judicious placement of stereocenters on precursors for 4 + 3 cycloaddition reactions can lead to high levels of stereocontrol in the 4 + 3 cycloaddition process of cyclopentenyl cations and tethered butadienes. This concept was successfully tested in the context of a synthesis of (+)-dactylol.

The intramolecular 4 + 3 cycloaddition (I4/3C) of allylic cations and dienes provides a rapid access to complex carbocyclic products from relatively simple starting materials.[1] Some time ago, both our group[2] and the West group[3] published data supporting the concept that the intramolecular 4 + 3 cycloaddition reaction of certain cyclopentenyl cations with tethered butadienes or furans could lead to 5−8 and 5−8−5 ring systems. For example, treatment of **1** with sodium trifluoroethoxide in trifluoroethanol afforded the 4 + 3 cycloadduct **2** in 61% yield as a 1:1 mixture of endo/exo isomers (Scheme 1).[4] Analogously, treatment of **3** with

Scheme 1



titanium tetrachloride afforded the cycloadducts **4a** and **4b** as a 2.7:1 mixture of stereoisomers (Scheme 2). The poor stereochemical control observed in these types of reactions appears to be fairly general and creates barriers to the application of the methodology in synthesis. As part of our continuing studies in this area, we are attempting to develop

† This paper is dedicated to Professor Norman Rabjohn on the occasion of his 85th birthday.

(1) For recent reviews of 4 + 3 cycloaddition chemistry, see: (a) Harmata, M. *Tetrahedron* **1997**, *53*, 6235. (b) Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, pp 41−86. (c) Harmata, M. In *Recent Research Developments in Organic Chemistry*; Transworld Research Network: Trivandrum, 1997; Vol. 1, pp 523−35. (d) Rigby, J. H; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (e) Cha, J.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217.

(2) Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241.

(3) (a) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795. (b) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876.

(4) Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860.

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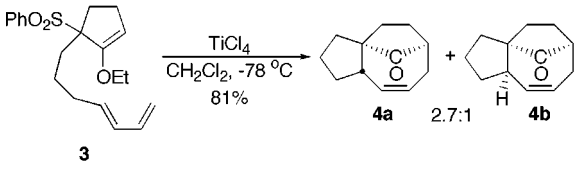
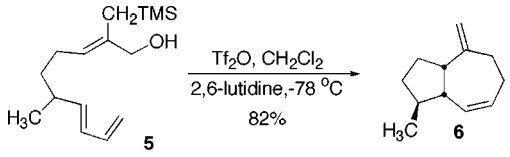
Scheme 2



strategies which will enable high levels of stereochemical control in reactions of this class. This report details some of our recent success in achieving our goals.

Our approach in performing highly stereoselective I4/3C reactions with cyclopentenyl cations was based on precedent established in both inter- and intramolecular 4 + 3 cycloaddition reactions. It is known that cyclopentenyl and cyclohexenyl cations bearing a stereogenic center react with dienes from their least-hindered faces, that is, on the face opposite the substituent.[5] In addition, Giguere and co-workers have established a dramatic effect of a dienylic substituent on the stereochemical outcome of an intramolecular 4 + 3 cycloaddition reaction.[6] This group reported that treatment of **5** with triflic anhydride at low temperature was shown to afford **6** as the major product of the reaction (isomer ratio: 92:5:3) (Scheme 3).

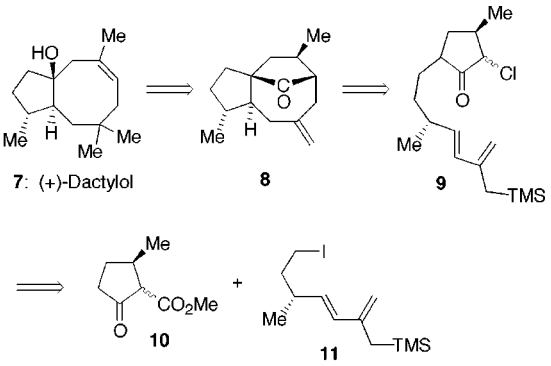
Scheme 3



We decided to explore the combination of these two stereochemical factors in the context of intramolecular 4 + 3 cycloaddition reactions of a cyclopentenyl cation. It soon became apparent that the natural product (+)-dactylol appeared to provide the ideal platform around which to conduct the study.

(+)-Dactylol is a cyclooctanoid sesquiterpene isolated from the sea hare *Aplysia dactylomela*.[7] A small number of total syntheses of both the racemic and enantiomerically pure forms of this compound have been reported, essentially as demonstrations of methodology capable of producing 5−8 fused ring systems.[8] Only one of these syntheses involved a cycloaddition process.[8e] Our retrosynthesis is shown in Scheme 4. Functional group manipulation of **8** was anticipated to lead to (+)-dactylol.

Scheme 4



We speculated that **8** could be obtained by cycloaddition of chloroketone **9**. The oxyallylic cation produced by the heterolysis of the corresponding enol or enolate was expected to cyclize via the transition state described by **12** (Figure 1), in accordance with the precedent discussed. The cycloaddition precursor was expected to be formed from the enantiomerically pure ketoester **10**, prepared in a straightforward fashion from (*R*)-pulegone, and iododiene **11**.[9,10] This meant using the stereogenic methyl-bearing center in **10** to effect stereocontrol. Although the stereogenic center on the five-membered ring would ultimately be destroyed to produce (+)-dactylol, the methyl substituent was still needed, and the source of the stereochemistry was inexpensive.

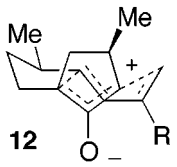


Figure 1.

The synthesis is shown in Scheme 5. Formation of the dianion from **10** and alkylation with **11** afforded **13** in 70% yield.[11] Removal of the carbomethoxy group was effected via a Krapcho procedure and gave the ketone **14** in 94% yield.[12] Past experience suggested that the chlorination of

(5) For some examples, see refs 1e and 3 and the following: (a) Hoffmann, H. M. R.; Wagner, D.; Wartchow, R. *Chem. Ber.* **1990**, *123*, 2131. (b) Hirano, T.; Kumagai, T.; Miyashi, T.; Akiyama, K.; Ikegami, Y. *J. Org. Chem.* **1991**, *56*, 1907. (c) Samuel, C. J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 736. (d) Hirano, T.; Kumagai, T.; Miyashi, T.; Akiyama, K.; Ikegami, Y. *J. Org. Chem.* **1991**, *56*, 1907.

(6) Giguere, R. J.; Tassely, S. M.; Rose, M. I.; Krishnamurthy, V. V. *Tetrahedron Lett.* **1990**, *31*, 4577.

(7) Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719.

(8) (a) Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123. (b) Paquette, L. A.; Ham., W. H.; Dime, D. S. *Tetrahedron Lett.* **1985**, *26*, 4983. (c) Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985**, *26*, 873. (d) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343. (e) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490. (f) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559. (g) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.

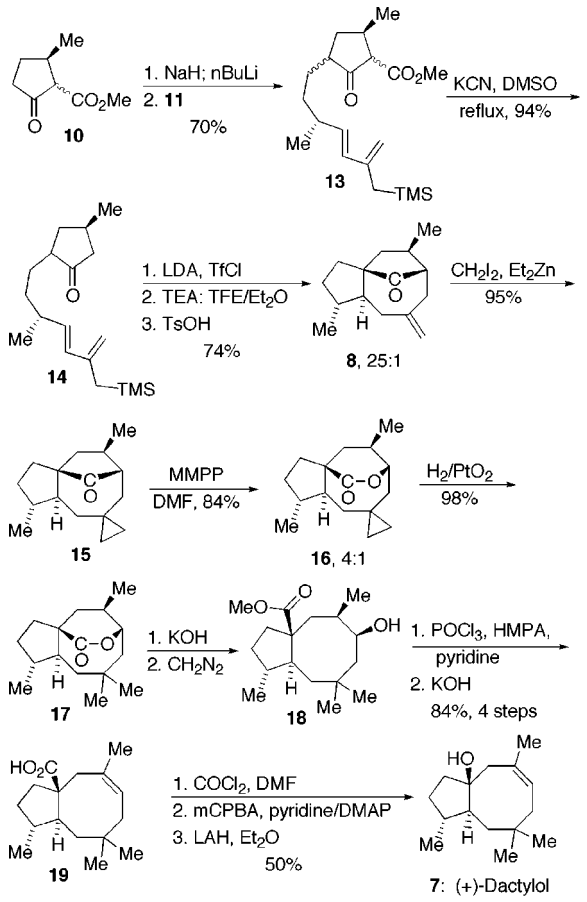
(9) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.

(10) Diene **11** was prepared using Evans' oxazolidinone chemistry. Details will be reported elsewhere.

(11) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(12) (a) Krapcho, A. P. *Synthesis* **1982**, 805. (b) Krapcho, A. P. *Synthesis* **1982**, 843.

Scheme 5



the ketone and cycloaddition steps could be coupled without any intervening purification. We also found that some desilylation with concomitant double bond migration occurred during the cycloaddition process, and therefore the crude cycloaddition product was subsequently desilylated using tosic acid. Thus, chlorination of the lithium enolate of **14** with triflyl chloride[13] followed by exposure of the resultant chloroketone to triethylamine in a 1:1 mixture of trifluoroethanol and ether gave a mixture which was treated with tosic acid to afford **8** in an overall yield of 74%. Most importantly, *compound **8** was formed as a mixture of two isomers in a ratio of 25:1*, supporting the model for the stereochemical outcome which we had developed.[14] This compares quite favorably with the diastereoselection observed by Giguere and co-workers in the preparation of **6**.

The major isomer was converted to (+)-dactylol. Application of the Simmons−Smith reaction afforded **15** in 95% yield. Interestingly, the Baeyer−Villiger reaction of **15** proceeded in an unexpected fashion.[15] Treatment of **15** with MMPP in DMF afforded a 4:1 mixture of two regioisomeric compounds, the major isomer being that which resulted from migration of the less substituted carbon atom. The factors influencing the regiochemistry of this reaction are under study. Separation and hydrogenation of the cyclopropane ring gave **17** in 98% yield. The structure and relative stereochemistry of **17** were established by single-crystal X-ray analysis.

Hydrolysis of **17** and esterification of the resulting hydroxy acid afforded hydroxy ester **18**. Installation of the double bond with the correct regiochemistry was accomplished using $POCl_3$ in HMPA.[16] Saponification of the ester then gave the corresponding acid. The overall yield for this four-step sequence was 84%.

Oxidative decarboxylation of **19** initially proved troublesome. We wanted to use a carboxy inversion beginning with the corresponding acid chloride,[17] but this compound was not easily prepared under standard conditions. We ultimately succeeded by using DMF and phosgene in refluxing toluene to effect complete acid chloride formation.[18] In the presence of pyridine and DMAP, this acid chloride reacted with mCPBA in benzene at room temperature to afford a mixed carbonate which upon reduction afforded (+)-dactylol in 50% overall yield from **19**. The spectral data, analytical data, and rotation of the sample were consistent with those published for dactylol.[7,8]

In summary, we have established a new approach to stereocontrol in intramolecular 4 + 3 cycloaddition reactions applicable to the synthesis of cyclooctanoids as demonstrated by a synthesis of (+)-dactylol. Further fundamental studies, applications, and new approaches to stereocontrol are under consideration and will be reported in due course.

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Supporting Information Available: ^1H and ^{13}C NMR for **7**−**8** and **14**−**19**. Tables of crystal data for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.

(14) The ratio was determined by integration of the olefinic region of a crude reaction mixture containing **8** and what appeared to be a single additional cycloadduct (500 MHz). This minor product has not been isolated or characterized.

(15) Reagent, ratio **16**:isomer, solvent, *T* (°C), time, yield: (a) mCPBA/$NaHCO_3$, 6:1, CH_2Cl_2, rt, 5 days, 67%; (b) $TFAA/H_2O_2$, 5:1, CH_2Cl_2, 0 °C−rt, 3 days, 36%; (c) mCPBA/TFA, 4:1, CH_2Cl_2, 0 °C−rt, 48 h, 53%; (d) peracetic acid/NaOAc, 9:1, AcOH, rt, 48 h, 31%; (e) MMPP, 4:1, DMF, rt, 48 h, 84%.

(16) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910.

(17) (a) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760. (b) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440. (c) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6893. (d) Majetich, G.; Hull, K. *Tetrahedron* **1987**, *43*, 5621.

(18) Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeier Reagents*; CRC: Boca Raton, 1994.