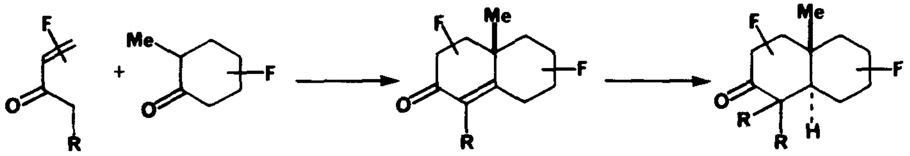
Tetrahedron Letters,Vol.24,No.42,pp 4529-4532,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A DIELS-ALDER APPROACH TO *TRANS*-FUSED, ANGULARLY METHYLATED DECALINS

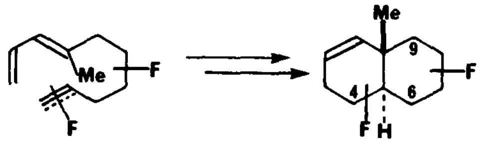
Steven D. Burke*, Tory H. Powner, and Masanori Kageyama
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Abstract: The title structures can be prepared by Diels-Alder cycloaddition of activated acetylenic or olefinic dienophiles tethered to a proximally-methylated butadiene unit.

The *trans*-fused decalin system bearing a single angular methyl group is a ubiquitous structural subunit in terpenoid and steroid natural products.[1] Classical synthetic approaches to these subunits have often relied upon the Robinson annulation, followed by reduction of the resultant enone to secure the *trans* ring junction (eq 1).[2] Obviously, these sequences can readily accommodate certain functionality patterns, while tolerating others less well. A popular complimentary strategy for the construction of six-membered rings is based upon the Diels-Alder reaction, especially in the intramolecular sense.[3] However, questions relating to reactivity and stereoselectivity remain unanswered for certain types of diene-dienophile pairings. Reported herein is a demonstration that the strategy generalized in eq 2 can serve as an entry to functionalized, *trans*-fused decalins which are angularly methylated.



(1)

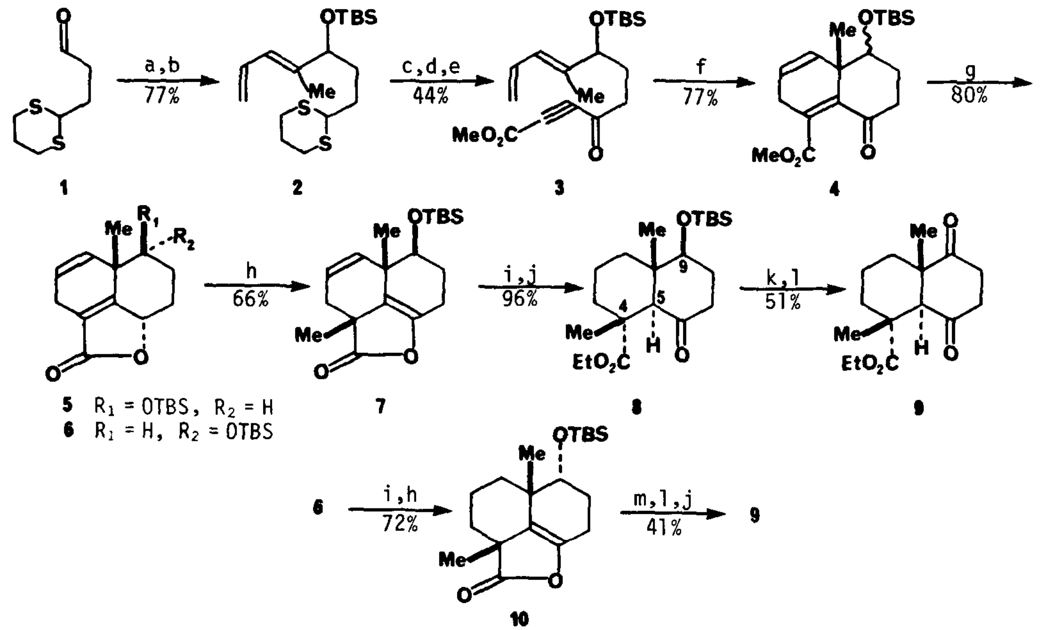


(2)

The basic question to be addressed was whether the Diels-Alder process would be thwarted by the incipient angular methyl group. For example, the intervention of 1,5-prototropic shifts along the methylated diene would compromise its regio- and stereochemical integrity.[4] Secondly, an unfavorable *s-cis*/*s-trans* equilibrium could increase the likelihood of competing processes, at the expense of the desired cycloaddition. Thirdly, an intolerance of functionality at the nascent C(4), C(6), and C(9) centers would diminish the ultimate usefulness of this approach. Finally, the direct accessibility of a *trans*-fused ring junction from such a cycloaddition process was far from assured.[5]

The first three of these four concerns were dismissed by the results shown in Scheme I.[6] Addition of (*Z*)-4-lithio-1,3-pentadiene[7] to aldehyde **1**[8] gave the expected allylic alcohol, which was directly converted[9] to the corresponding *t*-butyldimethylsilyl (TBS) ether **2** (77% from **1**). Thioacetal hydrolysis[10a] followed by 1,2-addition of the lithium acetylide derived from methyl propiolate to the unmasked aldehyde and Jones oxidation (0°C, 8 min) gave the acetylenic keto ester **3** in moderate overall yield. This substrate proved to be a willing participant in the desired cycloaddition. Thermolysis of **3** in toluene at 200°C for 11h provided in 77% yield a mixture (∼1:1) of the bicyclic keto esters **4**. Reduction of this mixture with ethanolic $NaBH_4$

SCHEME I[6]



[a](Z)-4-lithio-1,3-pentadiene, THF, -78°C. [b]TBSCl, imidazole, DMF, 25°C. [c]CH_3I, $CaCO_3$, CH_3CN/H_2O, reflux. [d]$LiC{\equiv}CCO_2Me$, THF, -78°C. [e]Jones oxidation, 0°C. [f]$PhCH_3$, methylene blue, 200°C, 11h. [g]$NaBH_4$, EtOH, 0°C. [h]LDA, THF/HMPA, -78°C; CH_3I, -78°→25°C. [i]H_2 (1 atm), PtO_2, EtOH. [j]K_2CO_3, EtOH, 25°C. [k]n-Bu_4NF, THF, 25°C. [ℓ]PCC, CH_2Cl_2, 25°C. [m]40% aq HF, CH_3CN, 25°C.

---

at 0°C gave the tricyclic lactones 5 (mp 113-114°C) and 6 (mp 122-123.5°C) in 38% and 42% yield, respectively.[11] The butenolide 5 was methylated at C(4) via the derived dienolate (LDA, THF/HMPA, -78°; CH_3I) to give the lactone 7 (mp 54-56°C) in 66% yield.[12] Catalytic hydrogenation [H_2 (1 atm), PtO_2, EtOH] followed by ethanolysis (K_2CO_3, EtOH) gave the bicyclic keto ester 8 (mp 112-113°C) in 96% yield. For the purpose of chemical correlation (vide infra), the TBS ether in 8 was cleaved (n-Bu_4NF, THF, 25°C) and the resulting secondary alcohol (mp 86-88°C) was oxidized with pyridinium chlorochromate (PCC)[13] to give the diketone 9 (mp 60-61°C) in 51% yield. The tricyclic butenolide 6 was also correlated with the diketone 9 via enol lactone 10 by the straightforward sequence shown.

In order to confirm the relative stereochemical assignments at C(4), C(5), C(9), and C(10) in 8, a single crystal was subjected to X-ray diffraction analysis.[14] The ORTEP[15] drawing shown in Figure I reveals the trans ring fusion, the equatorial deployment of the TBS ether substitutent, and the C(4) relative stereochemistry corresponding to that in numerous abietane, pimarane, and labdane diterpenes.[1]

It remained to determine whether the Diels-Alder step could directly provide a trans-fused, angularly methylated bicyclic system. For this purpose, an olefinic dienophile, rather than an acetylenic one as above, had to be tested. This was accomplished as shown in Scheme II.[6] Formylation of the anion derived from dithiane 11[16] with dimethylformamide[17] followed by Horner-Emmons olefination in refluxing benzene[18] gave the (E)-trisubstituted olefin 12 in 66% yield. Hydrolysis of the 1,3-dioxolane with aqueous HOAc and 1,2-addition of (Z)-4-lithio-

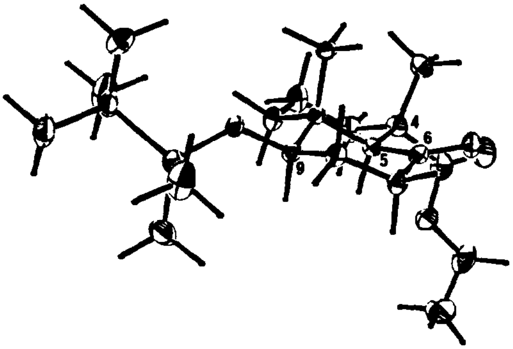
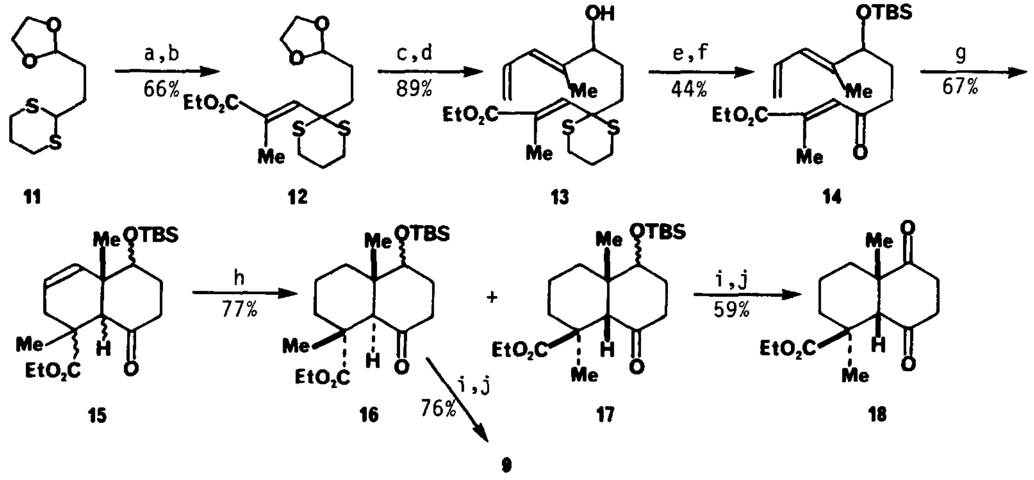


Figure I

1,3-pentadiene[7] to the aldehyde carbonyl gave the triene 13 (89%). Protection of the hydroxyl group as the TBS ether[9] and hydrolysis of the dithiane[10b] gave 14, which was thermolyzed in toluene in a sealed tube. After 72h at 280°C there was isolated in 67% yield a mixture of four compounds with the gross structure 15. Catalytic hydrogenation allowed the isolation of two pairs of compounds, represented by 16 (52%) and 17 (25%). Upon desilylation (n-Bu_4NF, THF, 25°C) and oxidation (PCC,[13] CH_2Cl_2, 25°C), the major pair (16) converged to a single product (mp 60-61°C) in 76% yield. This proved to be identical to the trans-fused diketone 9 from the earlier sequence (Scheme I). The minor pair of diastereomers (17) converged in similar fashion to a single substance (mp 57-58°C), which we assign as the cis ring fusion product 18.

SCHEME II[6]



[a] n-BuLi, THF, -78°C; DMF, -78°→-20°C. [b] $(EtO)_2PO\bar{C}MeCO_2Et$, PhH, reflux. [c] 60% aqueous HOAc, 70°C. [d] (Z)-4-lithio-1,3-pentadiene, $MgBr_2$, THF, -78°C. [e] TBSCl, imidazole, DMF. [f] HgO, $BF_3 \cdot Et_2O$, THF/H_2O, 25°C. [g] $PhCH_3$, BHT, 280°C, 72h. [h] H_2 (1 atm), PtO_2, EtOH, 25°C. [i] n-Bu_4NF, THF, 25°C. [j] PCC, CH_2Cl_2, 25°C.

Acknowledgment: We are grateful to the National Institutes of Health for generously supporting this research. High-field NMR spectra were obtained through the NSF Regional NMR Center at the University of South Carolina (Grant CHE 78-18723).

References and Notes

1. (a) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds", vol. II, Academic Press: New York, 1972. (b) "Natural Products Chemistry", vol. 1, Nakanishi, K.; Goto, T.; Itô, S.; Natori, S.; Nozoe, S., Eds., Academic Press: New York, 1974.
2. (a) Ref. 1(b). (b) "The Total Synthesis of Natural Products", vol. 2, ApSimon, J., Ed., John Wiley and Sons: New York, 1973.
3. For review articles surveying the intramolecular Diels-Alder reaction, see: (a) Oppolzer, W. Angew. Chem. Int. Ed. Engl. 1977, 16, 10. (b) Brieger, G.; Bennett, J. Chem. Rev. 1980, 80, 63.
4. (a) Borch, R. F.; Evans, A. J.; Wade, J. J. J. Am. Chem. Soc. 1977, 99, 1612. (b) Boeckman, R. K., Jr.; Alessi, T. R. Ibid. 1982, 104, 3216.
5. For examples of thermally-induced intramolecular Diels-Alder reactions wherein cis-fused octalin products predominate, see: (a) Roush, W. R.; Hall, S. E. J. Am. Chem. Soc. 1981, 103, 5200. (b) Taber, D. F.; Gunn, B. P. Ibid. 1979, 101, 3992. (c) Gras, J.-L.; Bertrand, M. Tetrahedron Lett. 1979, 4549. (d) Funk, R. L.; Zeller, W. E. J. Org. Chem. 1982, 47, 180. (e) Wilson, S. R.; Mao, D. T. Ibid. 1979, 44, 3093. (f) Joshi, B. S.; Viswanathan, N.; Gawad, D. H.; Balakrishnan, V.; Philipsborn, W. v. Helv. Chim. Acta 1975, 58, 2295. (g) Stork, G.; Clark, G.; Shiner, C. S. J. Am. Chem. Soc. 1981, 103, 4948. (h) Hirama, M.; Uei, M. Ibid. 1982, 104, 4251. For examples wherein trans-fused octalin products predominate, see: (i) Oppolzer, W.; Roberts, D. A.; Bird, T. G. Helv. Chim. Acta 1979, 62, 2017. (j) Wilson, S. R.; Mao, D. T. J. Am. Chem. Soc. 1978, 100, 6289. (k) Djuric, S.; Sarkar, T.; Magnus, P. Ibid. 1980, 102, 6885. (l) Funk, R. L.; Vollhardt, K.P.C. Ibid. 1979, 101, 215. (m) Nicolaou, K. C.; Barnette, W. E.; Ma, P. J. Org. Chem. 1980, 45, 1463. (n) Wilson, S. R.; Hague, M. S.; Misra, R. N. Ibid. 1982, 47, 747. (o) Kametani, T.; Nemoto, H.; Tsubuki, M.; Nishiuchi, M. Tetrahedron Lett. 1979, 27. (p) Refs. 5(a), 5(d). See also: (q) Oppolzer, W. Tetrahedron Lett. 1974, 1001. (r) Hall, S. E.; Roush, W. R. J. Org. Chem. 1982, 47, 4611.
6. All chiral substances were produced as racemates; a single enantiomer is shown for simplicity. All yields cited are for chromatographically pure substances. Structural assignments are supported by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis.
7. Piers, E.; Morton, H. E. J. Org. Chem. 1980, 45, 4263.
8. Prepared from acetal 11 by hydrolysis with 60% aqueous HOAc at 70°C for 18h in 98% yield. See ref. 16.
9. Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190.
10. (a) Vedejs, E.; Fuchs, P. L. J. Org. Chem. 1971, 36, 366. (b) Trost, B. M.; Preckel, M.; Leichter, L. M. J. Am. Chem. Soc. 1975, 97, 2224, and references cited therein.
11. The stereochemistry at C(6) in 5 and 6 is supported by the appearance of the butenolide C(6) methine hydrogen as a broad triplet with a primary coupling of 8.5 Hz in the ^{1}H NMR of each. For comparison, see: Fujita, E.; Uchida, I.; Fujita, T. J. Chem. Soc., Perkin Trans. I 1974, 1547.
12. For alkylation of a butenolide dienolate, see: (a) Hornfeldt, A. B.; Cederlund, B.; Jesperson, A. Acta Chem. Scand. 1971, 25, 3656. See also: (b) Eschenmoser, A.; Petrzilka, M.; Felix, D. Helv. Chim. Acta 1973, 56, 2950. (c) Kraus, G. A.; Roth, B. Tetrahedron Lett. 1977, 3129.
13. Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 2647.
14. The crystal structure data were acquired on an Enraf-Nonius CAD-4 diffractometer. The structure was solved by multisolution tangent refinement using MULTAN80. Calculations were done with the Enraf-Nonius Structure Determination package (Frenz, 1982). We are indebted to Dr. Lucas Lebioda of this Department for this structure determination.
15. Johnson, C. K. ORTEP II. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, 1970.
16. Acetal 11 was prepared in 77% yield by the reaction of 2-lithio-1,3-dithiane with 2-(2-bromoethyl)-1,3-dioxolane in THF/HMPA (-78°→0°C). See: Murai, A.; Ono, M.; Masamune, T. J. Chem. Soc., Chem. Commun. 1977, 573.
17. (a) Seuring, B.; Seebach, D. Justus Liebigs Ann. Chem. 1978, 2044. (b) Seebach, D.; Corey, E. J. J. Org. Chem. 1975, 40, 231.
18. (a) Johnson, M. R.; Kishi, Y. Tetrahedron Lett. 1979, 4347. (b) Nagaoka, H.; Kishi, Y. Tetrahedron 1981, 37, 3873.

(Received in USA 11 July 1983)