A [(4 + 2) + (3 + 2)] Approach to a Forskolin Intermediate; A Further Understanding of π-Facial Selection in Diels–Alder Reactions

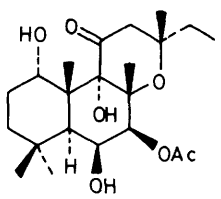
Alan P. Kozikowski,*[a] Sun Ho Jung,[a] and James P. Springer[b]

[a] *University of Pittsburgh, Department of Chemistry, Pittsburgh, Pennsylvania 15260, U.S.A.*
[b] *Merck Institute, Rahway, New Jersey 07065, U.S.A.*

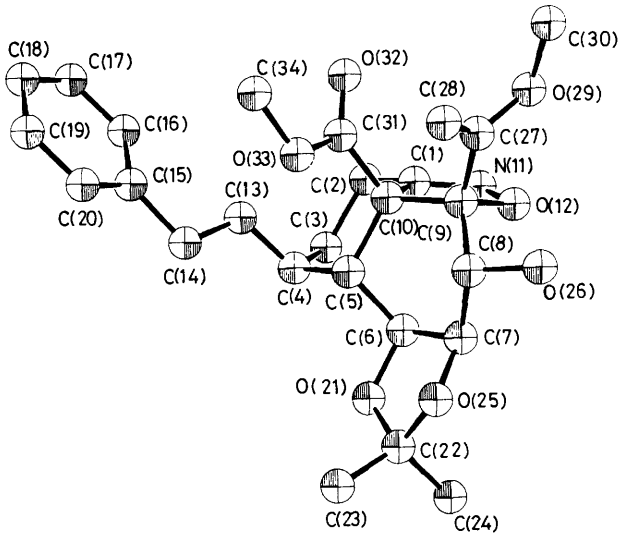
The preparation of a highly oxygenated decalin derivative suitable for use in the construction of the adenylate cyclase activator forskolin is described; the facial selectivity has been clarified by a crystal structure determination.

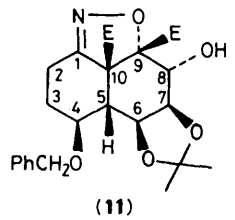
Forskolin is a structurally unique diterpene which can serve as an activator of adenylate cyclase, one of the major second messenger systems, either directly (at micromolar concentrations) or by high affinity binding to a GTP–binding protein–cyclase complex (GTP = guanosine triphosphate) (at nanomolar concentrations).[1] The potential for the development of new drug entities using forskolin as a prototype has led us to investigate the applicability of our recently reported [(4 + 2) + (3 + 2)] cycloaddition methodology[2] in the construction of this molecule. Herein we report the synthesis of a highly oxygenated decalin derivative suitable for further elaboration to forskolin. Additionally we comment on the nature and level of diastereoselection which accompany the reaction of a diene bearing an allylic asymmetric centre containing an oxygen substituent with an acetylenic dienophile.

The Diels–Alder diene required for this study was prepared



Forskolin





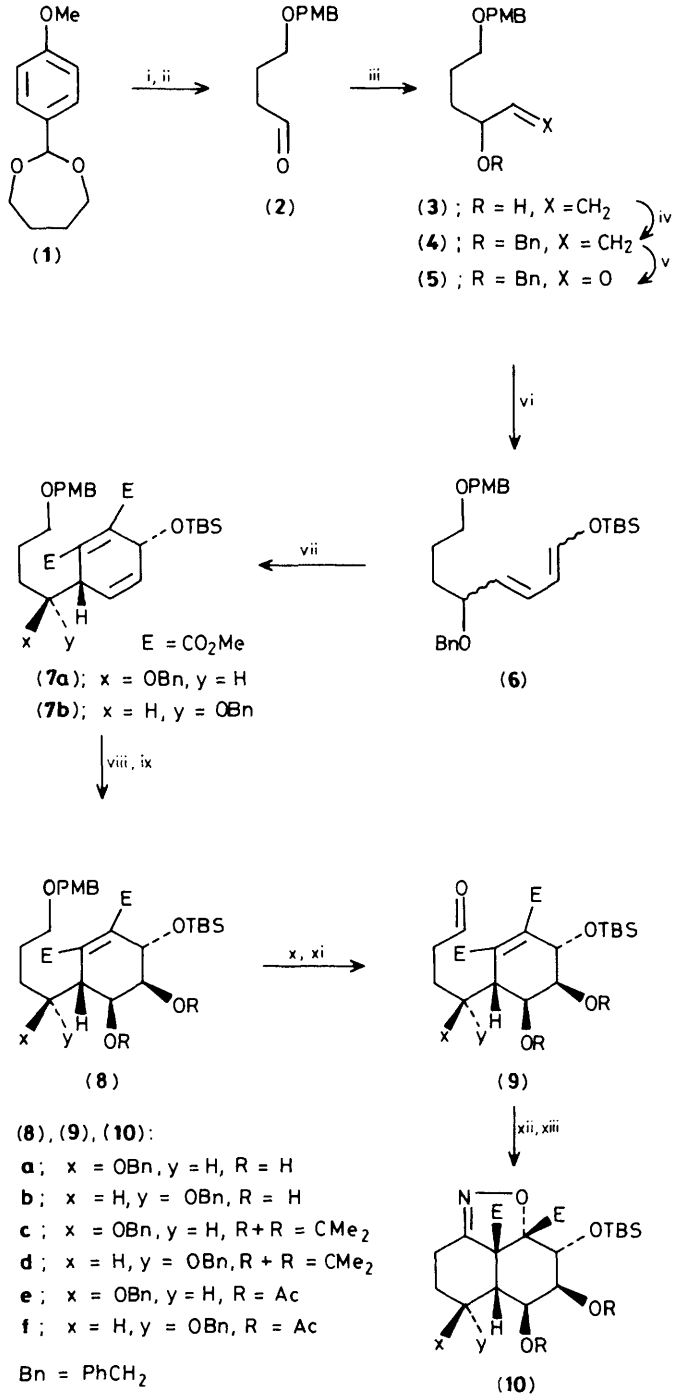
(11)

Figure 1. A single crystal *X*-ray analysis of alcohol (**11**) prepared from the major Diels–Alder cycloadduct (**7a**).

Figure 2. Transition states emphasizing the steric interactions between diene and acetylenic or ethylenic dienophile.

first from the *p*-methoxybenzyl (PMB) protected derivative of 4-hydroxybutanal *via* a sequence of steps involving vinylmagnesium bromide addition, benzyl ether formation, oxidative cleavage of the double bond to aldehyde, and Wittig reaction with (t-butyldimethylsilyloxy)allylidenetriethylphosphorane.[3] The major product of this Wittig reaction was the *E*,*E*-diene plus a mixture of the *E*,*Z*- and *Z*,*E*-dienes (*E*,*E*-diene/other dienes = 2/1).

This diene mixture was treated in turn with dimethyl acetylenedicarboxylate (DMAD), and the resulting diastereo-



Scheme 1. Synthesis of a forskolin intermediate. *Reagents*: i, $LiAlH_4$–$AlCl_3$, Et_2O, −78 °C, 2 h; ii, dimethyl sulphoxide (DMSO), $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C (86% for the two steps); iii, CH_2=CHMgBr, tetrahydrofuran (THF), room temp., 40 min (93%); iv, NaH, BnBr, THF, reflux, overnight (93%); v, OsO_4, $NaIO_4$, dioxane–H_2O–HOAc, room temp., overnight (86%); vi, Et_3P=CH–CH=CH–OSiBu^{t}Me$_2$, −78 °C to room temp. (68%); vii, DMAD, 120 °C, 4 h (41%); viii, OsO_4, NMO, acetone–H_2O, room temp., overnight; ix, dimethoxypropane, pyridinium *p*-toluenesulphonate (PPTS), CH_2Cl_2, room temp., 8 h (70% for the two steps); x, DDQ, CH_2Cl_2–H_2O, room temp., 2 h (83—95%); xi, PCC, CH_2Cl_2, room temp., 2 h (88%); xii, H_2NOH–HCl, pyridine, room temp., overnight (99%); xiii, NaOCl, xylenes–H_2O, 105—120 °C [66% yield of (**10c**) and 53% yield of (**10d**)].

isomeric cycloadducts (**7a**)/(**7b**) (2:1 ratio) originating from the *E,E*-diene were separated by column chromatography from the unreacted diene isomers. The cycloadducts were treated with osmium tetroxide and *N*-methylmorpholine *N*-oxide[4] (NMO) to provide a mixture of two diols separable by column chromatography. The separated diols were carried on individually through the following sequence of steps.

First, the vicinal diol unit of (**8a**) and (**8b**) was converted to its acetonide derivative. The PMB protecting group was next cleaved using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[5] and the deprotected alcohol was oxidized to aldehyde using pyridinium chlorochromate (PCC).[6] The aldehyde was derivatized as its oxime, and the oxime was exposed to sodium hypochlorite[7] to generate a single *cis*-fused isoxazoline in each case. By running the (3 + 2) cycloaddition reaction at 105—120 °C, (**10c**) and (**10d**) were obtained in yields of 66 and 53%, respectively. These same cycloadducts were obtained in yields of only 31 and 16%, respectively, when the intramolecular nitrile oxide cycloaddition (INOC) reaction was carried out at room temperature, a consequence presumably of competing dimer formation. By protecting the vicinal diol of (**8a**) and (**8b**) as a diacetate instead, the corresponding INOC products (**10e**) and (**10f**) were obtained in yields of 77 and 60%, respectively, in reactions carried out at room temperature and 70 °C, respectively.

Since the n.m.r. spectra of the isoxazolines (**10a**)—(**10d**) failed to reveal the stereochemical relationship of the C-4 centre relative to the other centres of asymmetry, a single crystal *X*-ray analysis† was carried out on the desilylated acetonide (**11**) derived from the 'major' Diels–Alder cycloadduct. As is apparent from the accompanying structure, a *syn* relationship exists between the C-4 oxygen substituent and the C-5 hydrogen. This *X*-ray result permitted us in turn to define the π-facial course of the Diels–Alder reaction.

Interestingly, the effect of the asymmetric oxygen-containing centre of the 'forskolin-diene' on the diastereofacial selectivity of the Diels–Alder reaction was identical to that found previously for the reaction of a threonine-derived diene containing an amine-bearing asymmetric centre in its cycloaddition with methyl propiolate.[8] These results taken together suggest that the dienophile and not the diene is responsible for the change in the π-facial course of the Diels–Alder reaction in comparison to the results obtained by Franck[9] and Carrié[10] using ethylenic dienophiles (here an *R* asymmetric centre on the diene directs an ethylenic dienophile to the *Re* face of the diene). Thus the original model proposed by Franck must be reformulated to include the possibility that an *R* asymmetric centre will direct an acetylenic dienophile to the *Si* face of the diene. We further suggest that this difference between the π-facial preference of ethylenic and acetylenic dienophiles derives from the feature that location of the heteroatom[11] in the outside position will involve a direct steric interaction of this substituent with the electron withdrawing group of the sp-hybridized dienophile. This steric interaction is, as illustrated in Figure 2, smaller for the sp^2-hybridized dienophile. Accordingly, the preferred transition state for the reaction of an acetylenic dienophile involves locating the heteroatom of the diene in an inside position and its R group *anti* to the incoming acetylene.[11,12]

In summary, the present results provide additional information regarding the influence of an allylic asymmetric centre on the π-facial course of the Diels–Alder reaction. The [(4 + 2) + (3 + 2)] cycloaddition process leads to an intermediate which contains all of the oxygen functionality required for the synthesis of forskolin. Additional steps involving *inter alia* introduction of the gem-dimethyl grouping and pyranone ring formation are required for completion of the work.

We are indebted to the National Institutes of Health for their support of these studies. We thank Professor Franck for several helpful discussions.

Received, 3rd February 1987;‡ Com. 127

References

1 P. F. Worley, J. M. Baraban, E. B. De Souza, and S. H. Snyder, *Proc. Natl. Acad. Sci., U.S.A.*, 1986, **83**, 4053.
2 A. P. Kozikowski, K. Hiraga, J. P. Springer, B. C. Wang, and Z. B. Xu, *J. Am. Chem. Soc.*, 1984, **106**, 1845.
3 A. P. Kozikowski and S. H. Jung, *J. Org. Chem.*, 1986, **51**, 3400.
4 V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
5 Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.
6 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
7 G. A. Lee, *Synthesis*, 1982, 508.
8 A. P. Kozikowski, T. R. Nieduzak, and J. P. Springer, *Tetrahedron Lett.*, 1986, **27**, 819; A. P. Kozikowski, T. Konoike, and T. R. Nieduzak, *J. Chem. Soc., Chem. Commun.*, 1986, 1350.
9 R. W. Franck, S. Argade, C. S. Subramaniam, and D. M. Frechet, *Tetrahedron Lett.*, 1985, **26**, 3187. Professor Franck has recently informed us that he has made similar observations regarding the change in π-facial selectivity for acetylenic dienophiles (R. W. Franck and R. Tripathy, unpublished results). Also, see: P. G. McDougal, J. G. Rico, and D. VanDerveer, *J. Org. Chem.*, 1986, **51**, 4494, and references therein.
10 R. Gree, J. Kessabi, P. Mosset, J. Martelli, and R. Carrié, *Tetrahedron Lett.*, 1984, **25**, 3697. The stereochemistry shown for the tetracyanoethylene adduct in this paper is incorrect. See: J. C. Messager and L. Toupet, *Acta. Crystallogr., Sect. B.*, 1986, **42**, 371.
11 For the location of a heteroatom substituent in the transition state of the nitrile oxide cycloaddition reaction, see: K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe, and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880; K. N. Houk, H.-Y. Duh, Y.-D. Wu, and S. R. Moses, *ibid.*, 1986, **108**, 2754. Also, see: E. Vedejs and C. K. McClure, *ibid.*, p. 1094; J. K. Cha, W. J. Christ, and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.
12 For other synthetic approaches to forskolin, see: P. R. Jenkins, K. A. Menear, P. Barraclough, and M. S. Nobbs, *J. Chem. Soc., Chem. Commun.*, 1984, 1423; K. C. Nicolaou and W. S. Li, *ibid.*, 1985, 421; F. E. Ziegler, B. H. Jaynes, and M. T. Saindane, *Tetrahedron Lett.*, 1985, **26**, 3307; Y. S. Kulkarni and B. B. Snider, *Org. Prep. Proced. Int.*, 1986, **18**, 7; P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, E. Polo, and D. Simoni, *J. Chem. Soc., Chem. Commun.*, 1986, 131; J. H. Hutchinson, G. Pattenden, and P. L. Myers, *Tetrahedron Lett.*, 1987, **28**, 1313; G. Bold, S. Chao, R. Bhide, S.-H. Wu, D. V. Patel, and C. J. Sih, *ibid.*, p. 1973; E. R. Koft, A. S. Kotnis, and T. A. Broadbent, *ibid.*, p. 2799.
13 Crystallographic programs used: MULTAN 80, P. Main, University of York, York, 1980; ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A., 1970; SDP Plus VI.I, Y. Oakaya and B. A. Frenz, B. A. Frenz and Associates, College Station, Texas, U.S.A., 1984.

† *Crystal data* for (**11**), $C_{24}H_{29}NO_9$, monoclinic, space group $P2_1/c$, a = 11.627(1), b = 14.797(1), c = 14.261(2) Å, β = 108.89(1)°, Z = 4, D_c = 1.360 g cm^{-3}. Of the 3119 unique reflections measured with an automatic four circle diffractometer using Cu radiation, 2413 were 'observed' with $I > 3\sigma(I)$. The structure was solved with a multi-solution tangent formula approach and difference Fourier analysis, and refined using full-matrix least-squares techniques[13] to R = 0.043. Hydrogen atoms were assigned isotropic temperature factors corresponding to their attached atoms.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

‡ Received in revised form 8th September 1987.