A STEREOSELECTIVE CONSTRUCTION OF A D-NORMORPHINAN RING SYSTEM

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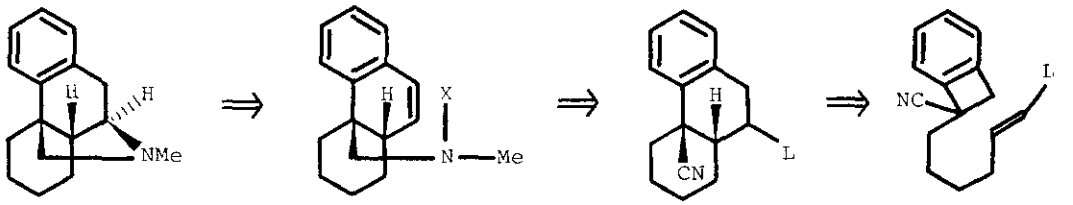
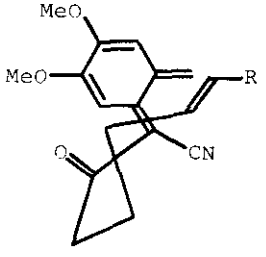
Abstract ——— An intramolecular Diels-Alder reaction of a benzocyclobutene derivative (7) afforded a tricyclic compound (8a), which was converted into a D-normorphinan derivative (13), stereoselectively.

Morphine alkaloids comprise a large and important family of natural products. Their chemistry has maintained the interests of a large number of synthetic organic chemists and spanned over many years.[1-3] As this class of alkaloids usually has B/C cis ring juncture in their molecules, we sought a general synthetic method for a construction of a morphinan ring system with a desired stereochemistry, and here wish to report a stereoselective synthesis of a D-normorphinan ring system.
Our synthetic design was based on an intramolecular cycloaddition reaction of a benzocyclobutene derivative to construct a B/C ring system having a cis ring juncture, followed by a D-ring formation employing a cyclization of an aminylium ion.

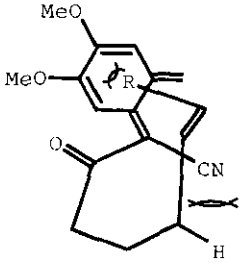


The requisite starting material (7) was prepared as follows. The benzocyclobutene (1)[4] was treated with 1-bromomethylcyclopent-1-ene (2)[5] in liquid ammonia and tetrahydrofuran in the presence of sodium amide at -34°C for 2 h to give the 1,1-disubstituted benzocyclobutene (3)[6] in 74.4 % yield. Lemieux oxidation of the olefin (3) with osmium tetroxide and sodium periodate yields the keto-aldehyde (4), whose treatment with thiophenol in methylene chloride in the presence of boron trifluoride etherate brought about the thioacetalization to afford the thioacetal

(5) in 86.3 % yield from 3. After the oxidation of the thioacetal (5) with 3 eq. molar of m-chloroperbenzoic acid, the sulfoxide (6) formed was thermally eliminated to give rise to the desired vinyl sulfone (7). An intramolecular Diels-Alder reaction of the vinyl sulfone (7) in refluxing o-dichlorobenzene for 4 h furnished the desired cycloadduct (8a) as a major product,[7] together with the trans-isomer (8b) in 57.3 % and 24.7 % yields, respectively. This stereoselectivity leading to the B/C cis ring system predominantly, could always be expected when a benzocyclobutene bearing a cyano group at the 1-position was subjected to an intramolecular [4+2]cycloaddition reaction,[8] and was rationalized by assuming that this reaction also proceeded via the transition state A rather than B in the least sterically hindered manner.

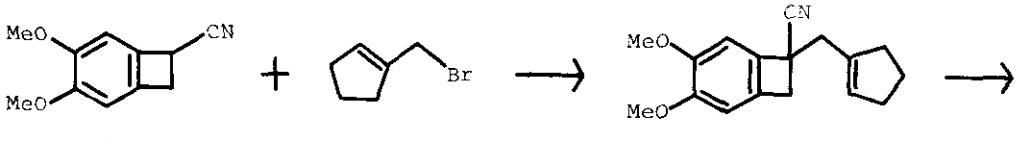


A

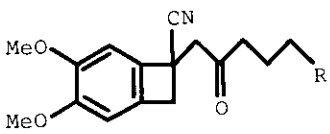


B

After the protection of the carbonyl group as its ketal, the adduct (9) was converted to the olefin (10)[9] by elimination of the sulfonyl group on treatment with potassium tert-butoxide in pyridine in 96.5 % yield. In order to accomplish the synthesis of D-normorphinan ring system, the olefinic nitrile (10) was treated with di-isobutylaluminum hydride in tetrahydrofuran to afford the aldehyde (11), whose treatment with methylamine followed by sodium borohydride reduction yielded the aminoolefin (12) in 75.3 % yield from 10. Finally, the D-ring formation was achieved by the cyclization of the aminylium ion[7,10] generated by treatment of the amine (12) with N-chlorosuccinimide, followed by silver oxide in aqueous tetrahydrofuran to give the D-normorphinan compound (13) in 25.1 % yield. The stereochemistry of the product (13) was confirmed based on its spectral data.[11] Thus, we could device the new stereoselective construction of the D-normorphinan ring system and this method would be applicable to the naturally occurring morphinan alkaloids.



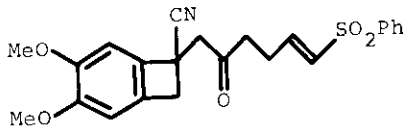
1 2 3



4 R=CHO

5 R=CH(SPh)$_2$

6 R=CH(SOPh)(SO$_2$Ph)



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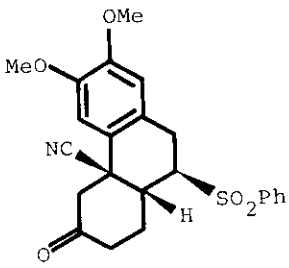
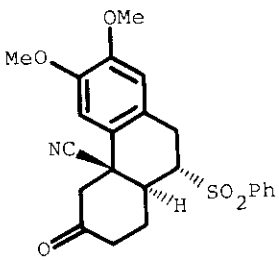
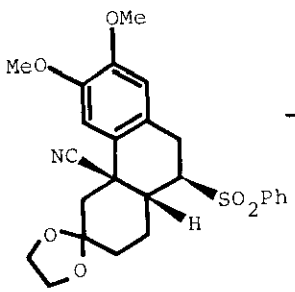


8a

+



8b



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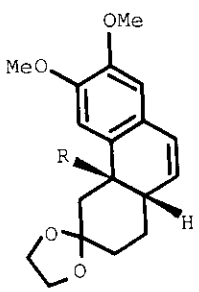
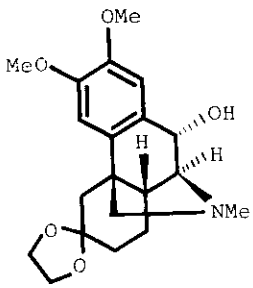


10 R=CN

11 R=CHO

12 R=CH$_2$NHMe



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2. G. Stork, "The Alkaloids" ed. by R.H.F. Manske, Academic Press, New York, Vol VI, pp 219 - 246 (1960).
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4. T. Kametani, K. Ogasawara, and T. Takahashi, Tetrahedron, 1973, 29, 73.
5. P.R. Pal, C.G. Skinner, R.L. Dennis, and W. Shive, J. Am. Chem. Soc., 1956, 78, 5116.
6. All the new compounds prepared gave the satisfactory elemental analyses and was fully characterized by the spectral data.
7. The stereochemistry of the adducts (8a and 8b) could not be determined at this stage, and was confirmed on the basis of the nmr spectrum of the amine (12); ($CDCl_3$) δ 2.30 (3H, s, >NMe), 3.80 and 3.83 (each 3H, each s, 2 x OMe), 5.72 (1H, dd, J=5 Hz, 10 Hz, ArCH=C<u>H</u>-), 6.26 (1H, d, J=10 Hz, ArC<u>H</u>=CH-), 6.54 and 6.93 (each 1H, each s, 2 x ArH). see: T.T. Conway, T.W. Doyle, Y.G. Perron, J. Chapuis, and B. Belleau, Can. J. Chem., 1975, 53, 245.
8. K. Shishido, S. Shimada, K. Fukumoto, and T. Kametani, Chem. Pharm. Bull. (Tokyo), 1984, 32, 922.
9. Compound 10; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2250. NMR ($CDCl_3$) δ 3.94 - 3.12 (1H, m, >C=CH-C<u>H</u><), 3.89 and 3.94 (each 3H, each s, 2 x OMe), 5.54 (1H, dd, J=10 Hz, 2 Hz, ArCH=C<u>H</u>-), 6.47 (1H, dd, J=10 Hz, 3 Hz, ArC<u>H</u>-), 6.63 and 7.11 (each 1H, each s, 2 x ArH). MS m/e 327 (M^+). High MS Calcd for $C_{19}H_{21}NO_4$ m/e 327.1470 (M^+). Found m/e 327.1470 (M^+).
10. L. Stella, Angew. Chem. Int. Ed. Engl., 1983, 22, 337.
11. Compound 13; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3350. NMR ($CDCl_3$) δ 2.54 (3H, s, >NMe), 3.20 (1H, dd, J=3 Hz, 5 Hz, >N-C<u>H</u><), 3.86 and 3.87 (each 3H, each s, 2 x OMe), 4.55 (1H, d, J=3 Hz, >C<u>H</u>-OH), 6.86 and 6.91 (each 1H, each s, 2 x ArH). MS m/e 361 (M^+). High MS Calcd for $C_{20}H_{27}NO_5$ m/3 361.1887 (M^+). Found m/e 361.1882 (M^+).

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