A NOVEL STEREOSELECTIVE SYNTHESIS OF MORPHINAN SKELETON

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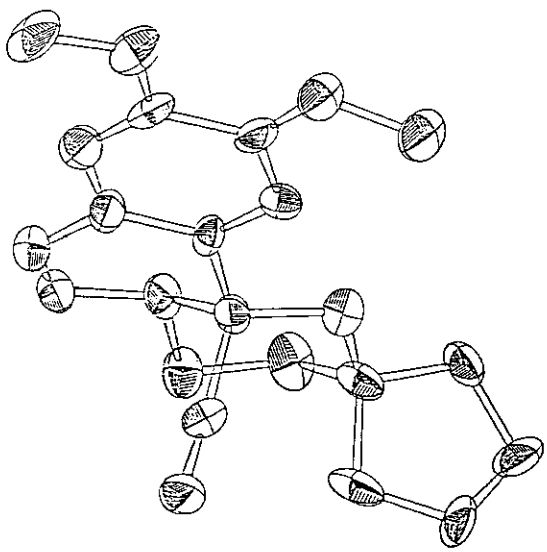
Abstract ——— A basic skeleton of morphinan alkaloids was stereoselectively synthesized by employing a thermolysis of a benzocyclobutene derivative.

Recently, we have succeeded[1] in a stereoselective construction of a D-normorphinan ring system utilizing an intramolecular Diels-Alder reaction of a benzocyclobutene derivative as a key step. As an extension of the above work, we have further investigated to seek a general route to morphinan alkaloids, and here wish to report a novel and stereoselective synthesis of a basic skeleton of morphinan alkaloids. 1-Cyano-4,5-dimethoxybenzocyclobutene (1)[2] was treated with the olefinic bromide (2)[3] in dimethylformamide in the presence of sodium hydride to afford the olefinic benzocyclobutene (3) in 72.4 % yield. The thermolysis of 3 in refluxing xylene for 3 h furnished the adducts 4 and 5, in 60.7 % and 29.3 % yields, respectively. Based on the spectroscopic data of the adducts (4 and 5), both compounds were deduced to be stereoisomers. The major tricyclic compound (4) was then converted to the olefin (6)[4] in 77.8 % yield by treatment with N-bromosuccinimide and benzoyl peroxide in refluxing carbon tetrachloride for 20 min. The similar treatment of the minor tricyclic cyanide (5) yielded the olefin (7),[5] in 72.5 % yield, whose stereochemistry was confirmed by its X-ray analysis[6] to have a B/C-trans ring juncture (Figure). Hence the major one was assigned to be the B/C-cis isomer, whose ring juncture was usually presented in naturally occurring morphinan alkaloids. In order to construct a D-ring, the desired B/C-cis compound (6) was reduced with di-isobutylaluminum hydride in tetrahydrofuran to give the aldehyde (8) in 78.8 % yield. The elongation of a methylamine moiety was achieved as follows. The treatment of the aldehyde (8) with nitromethane in isopropanol in the presence of potassium fluoride and 18-crown-6 at ambient temperature, followed by dehydration with acetic anhydride and N,N-dimethylaminopyridine afforded the nitro-

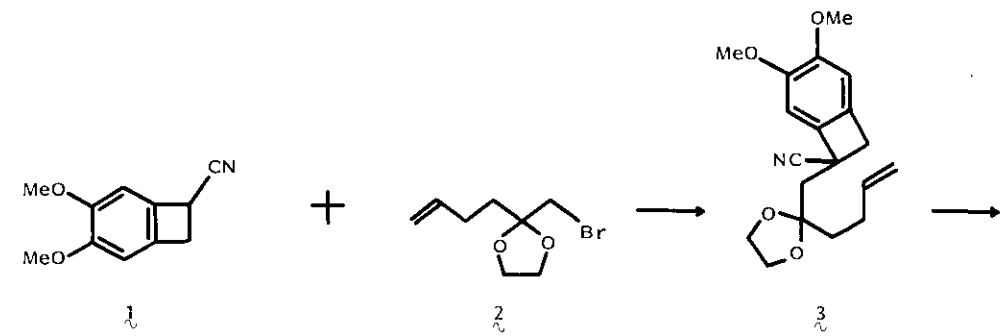
olefin (9) in 96.8 % yield. The reduction of 9 with sodium borohydride in ethanol gave the nitro compound (10), whose lithium aluminum hydride reduction, followed by acylation with methyl chloroformate gave rise to the urethane (11), in 54 % yield from 9. The urethane (11) was again reduced with lithium aluminum hydride to afford the amine (12) in 62.9 % yield. Finally, the D-ring was constructed by treatment of 12 with N-chlorosuccinimide in methylene chloride at 0 °C, and successively with silver oxide in methanol, via the amilynium ion intermediate to give 13[7] in 50.9 % yield.

Thus, we could synthesize a morphinan ring system from the readily available benzocyclobutene derivative, and this synthetic route would provide a general route to morphinan alkaloids.

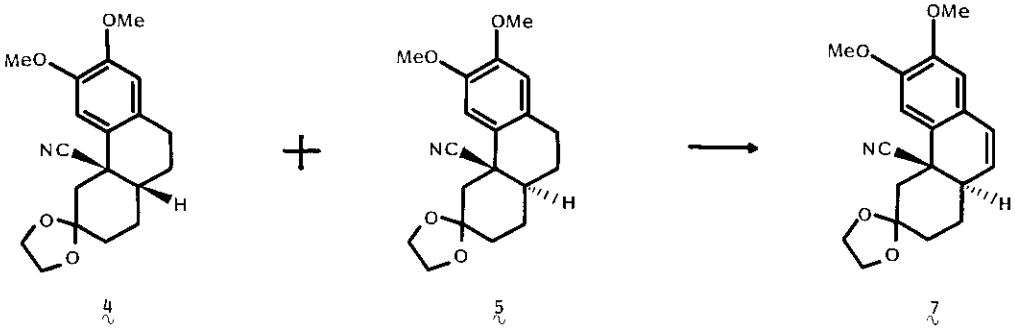


Figure

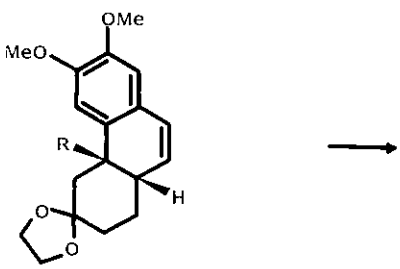
Molecular Structure of One of Enantiomers of the Tricyclic Olefin (7).



1 2 3



4 5 7



6 R=CN

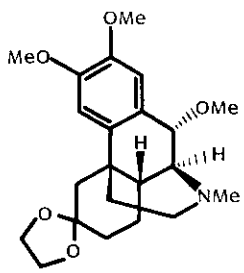
8 R=CHO

9 R=CH=CH-NO_2

10 R=$CH_2CH_2NO_2$

11 R=$CH_2CH_2NHCO_2Me$

12 R=CH_2CH_2NHMe



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REFERENCES

1. T. Kametani, Y. Suzuki, and T. Honda, Heterocycles, 1985, 23, 305.
2. T. Kametani, K. Ogasawara, and T. Takahashi, Tetrahedron, 1973, 29, 73.
3. The bromide (2) was prepared from 2-(but-3-enyl)-2-methyl-1,3-dioxolane by treatment with pyridinium bromide perbromide in tetrahydrofuran at ambient temperature for 2 h.
4. IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2250. NMR ($CDCl_3$) δ 3.89 and 3.94 (each 3H, each s, 2 x OMe), 5.54 (1H, dd, J=10 Hz, 2 Hz, ArCH=CH-), 6.46 (1H, dd, J=10 Hz, 3 Hz, ArCH=CH-), 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^+).
5. IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2240. NMR ($CHCl_3$) δ 3.89 and 3.90 (each 3H, each s, 2 x OMe), 5.80 (1H, dd, J=10 Hz, 2 Hz, ArCH=CH-), 6.58 (1H, dd, J=10 Hz, 2 Hz), 6.72 and 6.78 (each 1H, each s, 2 x ArH). MS m/e 327 (M^+). Anal. Calcd $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found; C, 79.71 H, 7.45; N, 4.08. mp 194 - 195°.
6. Monoclinic, space group P 21/C with a=12.9507 (33), b=10.2787 (20), C=20.8713(55)Å; D_{calc}=1.28 g/cm for Z=4. Final R value was 0.093 for 835 observed reflections.
7. NMR ($CDCl_3$) δ 2.87 (3H, s, NMe), 3.54 (3H, s, OMe), 3.79 and 3.83 (each 3H, each s, 2 x OMe), 4.30 (1H, s, ArCHOMe), 6.70 and 6.76 (each 1H, each s, 2 x ArH). MS m/e 389 (M^+). High MS Calcd for $C_{23}H_{31}NO_5$ m/e 389.2022. Found m/e 389.2022.

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