Tetrahedron Letters,Vol.25,No.31,pp 3335-3338,1984 0040-4039/84 $3.00 + .00
printed in Great Britain

AN EXPEDIENT AND SELECTIVE ROUTE TO CROWNED MORPHINE AND ISOMORPHINE CONGENERS. A PROBE FOR IONOPHORE AND MOLECULAR RECOGNITION OF OPIATE RECEPTOR

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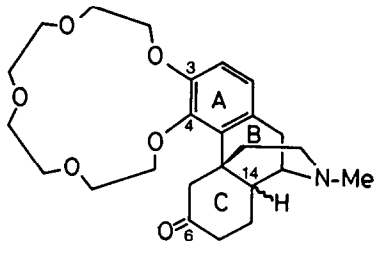
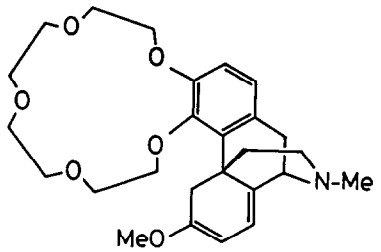
Abstract: The first and expedient syntheses of 3,4-crowned[15-crown-5] trans- and cis-6-morphinanones (1a and 1b) starting from thebaine and dihydrocodeinone, respectively, are described.

It has been suggested that the mechanisms of action of opiates and the transmission of pain are closely related to sodium ion transport processes in opioid receptor membranes.[1] A brilliant and rather daring hypothesis was recently advanced by Snyder et al. that the opioid receptor can exist in two conformations allosterically modulated by sodium ion, the "agonist" and "antagonist" conformations.[2] Therefore, we felt that this hypothesis could be directly tested by introducing the ionophore function into opiate molecules by intramolecular incorporation of crown ethers. In this commumication we report the first and expedient syntheses of 3,4-crowned[15-crown-5] trans- and cis-6-morphinanones (1a and 1b).[3] These compounds may serve as a new type of ligands for elucidation of the mechanisms of action of opiates.

The synthesis of 1a was performed via crowned thebaine (2) which can be regarded as a potential synthetic precursor of crowned morphine and its congeners.[4] We started its synthesis from thebaine (3)[5] initially converting



1a: α-H14 (B/C trans)
1b: β-H14 (B/C cis)



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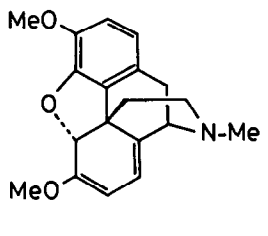

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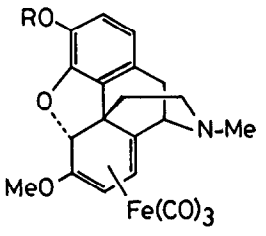
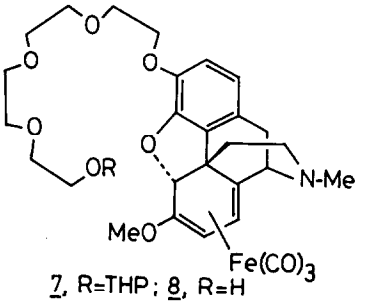
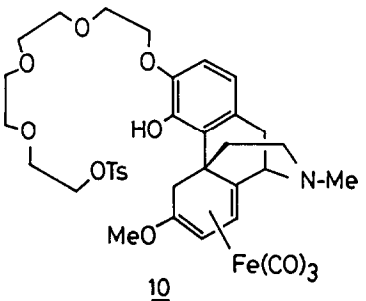


4, R=Me
5, R=H



7, R=THP; 8, R=H
9, R=Ts



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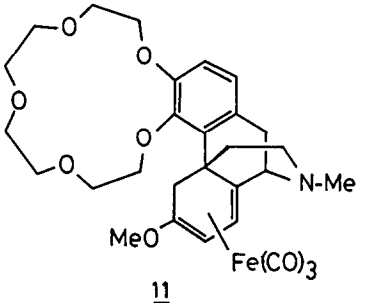

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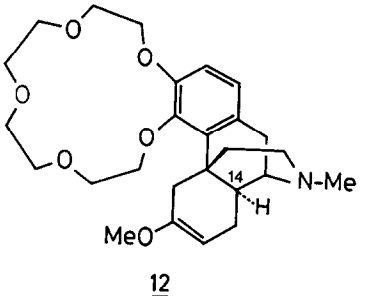

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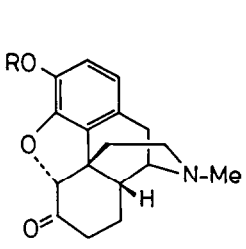
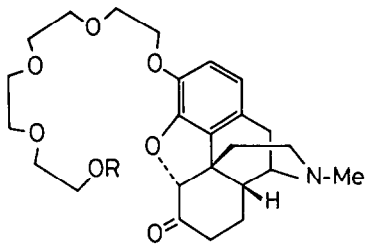
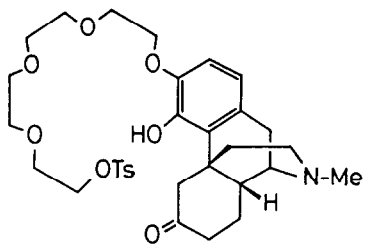
to the tricarbonyliron complex 4[6] since 3 is labile agaist strong acid and base treatments. Demethylation (excess $BBr_3/CHCl_3$) of 4 led to 80% yield of phenol 5[7] [mp 179-184°C (dec.)], which was condensed with 1-(toluensulfonyloxy)-11-[(tetrahydropyran-2-yl)oxy]-3,6,9-trioxaundecane (6) to afford 7 in 67% yield (NaH/dry DMF). Compound 7 was converted into the tosylate 10 in 71% yield in three steps: acid hydrolysis (p-TsOH/C_6H_6-H_2O; 8), tosylation (p-TsCl/DMAP/CH_2Cl_2; 9) and reductive cleavage of 4,5-oxide bridge (Zn/AcOH).[6] The construction of crown ether ring was accomplished by employing high dilution method. Addition of the dry DMF solution of 10 to the suspension of oil-free NaH in dry DMF over 12 h afforded the cyclization product 11[7] in 54% yield. Decomplexation of 11 with trimethylamine oxide in dry C_6H_6 gave the crystalline 2[8] (mp 128-132°C) in 78% yield. Catalytic hydrogenation of 2 in the presence of tristriphenylphosphine rhodium chloride in C_6H_6[9] gave enolether 12[7] (68%) as a sole product, which was clearly indicated to be a 8,14-dihydro compound by ^{1}H-NMR spectrum. Then, treatment of 12 with 10% HCl in THF afforded 1a as a viscous oil in 85% yield: MS m/e (%) 445 [M^+] (96), 388 (27), 285 (10), 164 (80), 122 (27); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.64-3.32 (m, 14H), 2.33 (s, 3H, NCH_3), 3.60-4.26 (m, 16H, crown ether moiety), 6.75 (s, 2H, H-1 and 2); Anal. Calcd for $C_{25}H_{35}NO_6$: 445.2464. Found: 445.2478; $[\alpha]_D^{21}$ -28.8 (c 1.45, $CHCl_3$). While 1a was shown to be homogeneous by TLC and spectral analysis, the stereochemistry of C-14 remained obscure at this stage.



13, R=Me
14, R=H



15, R=THP
16, R=H



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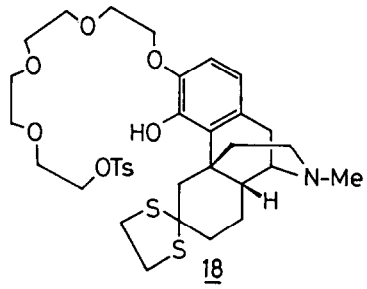

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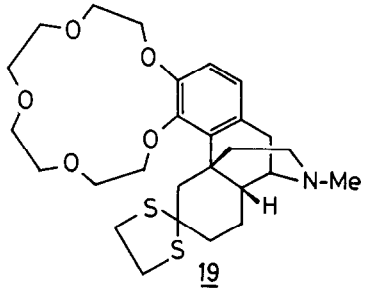

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Therefore, we decided to synthesize 1b starting from dihydrocodeinone (13) whose stereochemistry at C-14 is firmly established. Similarly, demethylation ($BBr_3/CHCl_3$, 73%, 14), condensation with 6 (NaH/dry DMF, 72%, 15), and acid hydrolysis (c-HCl/THF, 100%) gave alcohol 16.[7] Reductive cleavage of 4,5-oxide bridge (Zn/NH_4Cl/n-propanol)[10] of 16 followed by tosylation (p-TsCl/pyridine) yielded the phenol 17 in 73% yield. Attempted cyclization of 17 was unsuccessful presumably due to the presence of enolizable protons under the reaction conditions. Therefore, the carbonyl group of 17 was protected as thioketal 18 (ethandithiol/$BF_3 \cdot Et_2O$/AcOH, 82%), which was smoothly converted to 19[7] (55%) by treating with NaH in dry DMF (high dilution). Finally, removal of the protecting group [$Tl(NO_3)_3 \cdot 3H_2O$/THF-MeOH][11] completed the synthesis of 1b (84%).[12]

Compounds 1a and 1b show apparently different Rf values in TLC [SiO_2, $CHCl_3$-MeOH(4:1)]: 1a;0.34, 1b;0.20, indicating the different stereochemistry of the B/C ring junction in 1a (trans) and 1b (cis). This is also supported by the characteristically different fragmentation patterns in their mass spectra.[13] The stereoselective formation of novel 1a possessing the unnatural configuration at C-14 is apparently a result of α-face selective hydrogenation of crowned thebaine (2).[14]

Compound 1b was shown to possess an extractability (4.9%) of sodium ion by the UV-spectroscopy. The biological activity and the full details of the affinity for alkali metal ions of these compounds will be reported in near future.

References and notes.

(1) Snyder, S.H. Scientific American, 1977, 236, No.3, 44.

(2) Feinberg, A.P.; Creese, I.; Snyder, S.H. Proc. Nalt. Acad. Sci. USA, 1976 73, 4215.

(3) The reaction of morphine with 1,11-dichloro-3,6,9-trioxaundecane was reported to give only the open-chain ether derivatives: Frensch, K.; Vögtle, F. Liebigs Ann. Chem., 1976, 2118.

(4) The conversions of thebaine (3) into various morphine congeners are well established: (a) Dauben, W.G.; Baskin, C.P.; von Riel, H.C.H.A. J. Org. Chem., 1979, 44, 1567. (b) Bentley, K.W.; Hardy, D.G.; Meek, B. J. Am. Chem. Soc., 1967, 89, 3273. (c) Lutz, R.E.; Small, L. J. Org. Chem., 1936, 4, 220.

(5) Hayakawa, K.; Motohiro, S.; Fujii, I.; Kanematsu, K. J. Am. Chem. Soc., 1981, 103, 4605.

(6) Birch, A.J.: Fitton, H. Aust. J. Chem. 1967, 22, 971.

(7) Satisfactory IR, ^{1}H-NMR and mass spectra were obtained for all new compounds. Analytical data for some of them were obtained by high resolution mass spectra. Most of the compounds were purified by silica gel chromatography, as evidenced by TLC analysis.

(8) Compound 2: MS m/e(%) 457 [M^+] (100), 398 (8), 239 (13) 105 (24); ^{1}H-NMR ($CDCl_3$) δ 1.62-2.62 (m, 4H), 2.44 (s, 3H, NCH_3), 2.85-3.35 (m, 5H), 3.57 (s, 3H, OCH_3), 3.67-3.98 (m, 12H, $-CH_2O-$), 4.04-4.32 (m, 4H, $-CH_2OPh$), 4.86 (d, J=6 Hz, H-8), 5.84 (d, J=6 Hz, H-7), 6.76 (s, 2H, H-1 and 2). The IR ($CHCl_3$) spectrum showed no bands due to tricarbonyliron moiety. Anal. Calcd for $C_{26}H_{35}NO_6$: 457.2463. Found: 457.2413; $[\alpha]_D^{21}$ +130.2 (c 0.9, $CHCl_3$).

(9) Birch, A.J.; Walker, K.A.M. J. Chem. Soc.(C), 1966, 1894.

(10) Brossi,A.; Atwell, L.; Jacobson, A.E.; Rozwadowska, M.D.; Flippen-Anderson, J.L.; Gilardi, R. Helv. Chim. Acta, 1982, 65, 2394.

(11) Fujita, E.; Nagao, Y.; Kaneko, K. Chem. Pharm. Bull., 1978, 26, 3743.

(12) Compound 1b: MS m/e(%) 445 [M^+] (41), 386 (6), 285 (9), 164 (100), 59 (18); IR ($CHCl_3$) 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.12-2.60 (m, 11H), 2.48 (s, 3H, NCH_3), 2.74-3.22 (m, 3H), 3.55-4.41 (m, 16H), 6.74 (s, 2H, H-1 and 2); Anal. Calcd for $C_{25}H_{35}NO_6$: 445.2464. Found; 445.2462; $[\alpha]_D^{21}$ -19.6 (c 2.3, $CHCl_3$).

(13) While 1a (trans) shows an intense molecular ion peak, 1b (cis) reveals a relatively weak molecular ion peak and the characteristic fragment peak at m/e 59: Mandelbaum, A.; Ginsburg, D. Tetrahedron Lett., 1965, 2479.

(14) This is a sharp contrast to the well-known β-face selectivity of thebaine and can be attributed to its conformational change caused by the 4,5-oxide bridge cleavage. Recently, a similar reversal of stereoselectivity was observed in the reaction of β-dihydrothebaine: Ghosh, A.C.; Portlock, D.E.; Dalzell, H.C.; Malmberg, C.; Herlihy, P.; Razdan, R.K.; Duax W.L.; Smith, G.E. J. Org. Chem., 1983, 48, 4137.

(Received in Japan 14 April 1984)