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Synthesis of opioid ligands having oxabicyclo[2.2.2]octane and oxabicyclo[2.2.1]heptane skeletons

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Abstract—Two types of novel skeletons were synthesized from morphinan and 4,5-epoxymorphinan derivatives by using stable and unstable sulfur ylide.

Buprenorphine[1] and etorphine[2] are potent μ and ε opioid analgesics, and like opiate analgesics in general, they can cause serious respiratory depression. However, these two particular analgesics produce an especially dangerous form of respiratory depression that cannot be reversed by the μ opioid antagonist naloxone.[1] This resistance to naloxone antagonism is generally attributed to the high affinity of these opiates for the μ receptor and to their high lipophilicity.[1,3]

TAN-821 is a potent and selective ε opioid receptor agonist that produces strong analgesia in vivo.[4] However, it is not selective enough for the ε receptor and in fact has been found to bind in vitro (mouse vas deferens assay) to the μ opioid receptor type.

These three compounds share a common 6,14-endoethanotetrahydrothebaine skeleton with a 7,8-methylene bridge (**1**). We hypothesized that the strong affinity of these compounds for μ opioid receptor may derive in part from the high lipophilicity conferred by this bridge. If so, introduction of a hydrophilic group should reduce their affinity for μ opioid receptor. We therefore designed a novel compound with hydrophilicity at its bridge position, namely, 17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-8-oxa-6,14-endoethanomorphinan (**2**), to improve the ε selectivity of TAN-821 in vitro (Fig. 1).

On the basis of the above discussion, we have previously synthesized a novel acetal (**3**) with a 17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-8-oxa-6,14-endoethanomorphinan skeleton.[5] However this compound was not stable, with facile opening of the ether ring that afforded the corresponding hydroxy aldehyde (**4**).

Therefore we sought to synthesize stable basic skeleton **2**, and in the course of these studies, we developed new synthetic methods for oxabicyclo[2.2.2]octane (**2**) and oxabicyclo[2.2.1]heptane skeleton (**5**) (Fig. 2).

Here we report the new synthetic methods for the two skeletons using two types of sulfur ylides.

As 6-keto group of naltrexone is accessible to nucleophilic attack from the β side to give an α alcohol derivatives, we tried to obtain 6-α-epoxide of naltrexone derivative (**7**) by use of a stable sulfur ylide derived from trimethylsulfoxonium iodide.[6] The α epoxide (**7**) was expected to convert to the objective oxabicyclo-[2.2.2]octane derivative (**2**), however, only β epoxide (**6**) was obtained in 67% yield, but not the objective α epoxide (**7**) (Scheme 1).

Although nucleophilic attack occurred from the β side of naltrexone methyl ether, we speculated that the kinetically formed α hydroxy intermediate (**8**) was returned to the original ketone because of the strong dipole–dipole interaction between 4,5-epoxy ring and the resulting α hydroxy group. Ultimately, nucleophilic attack of the reagent occurred from the α side because of reversible

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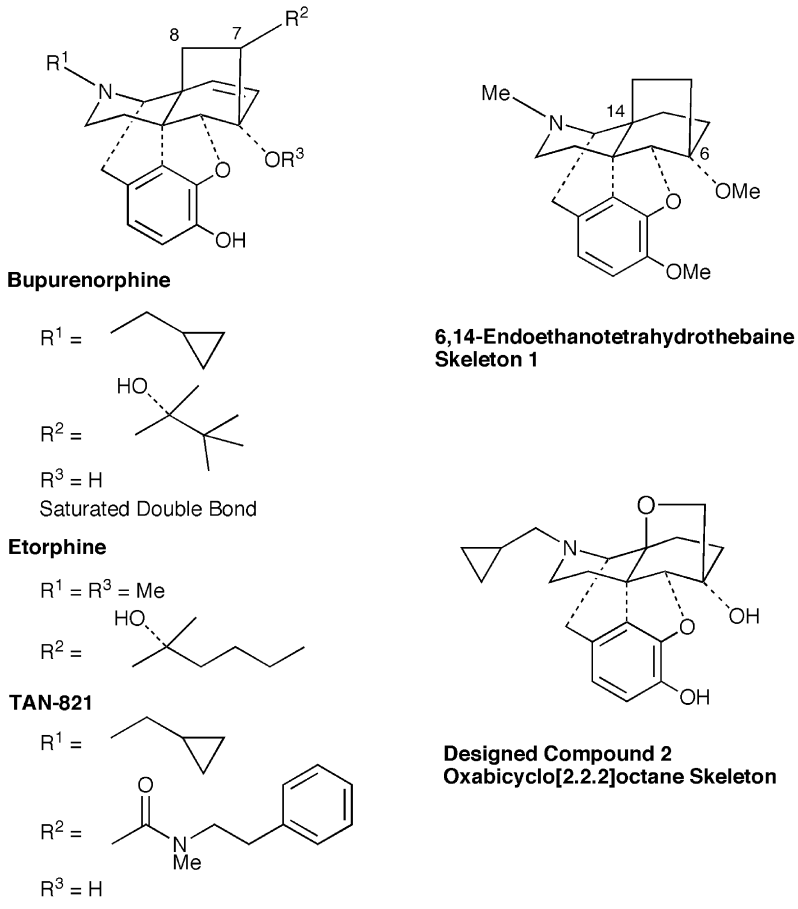


Figure 1.

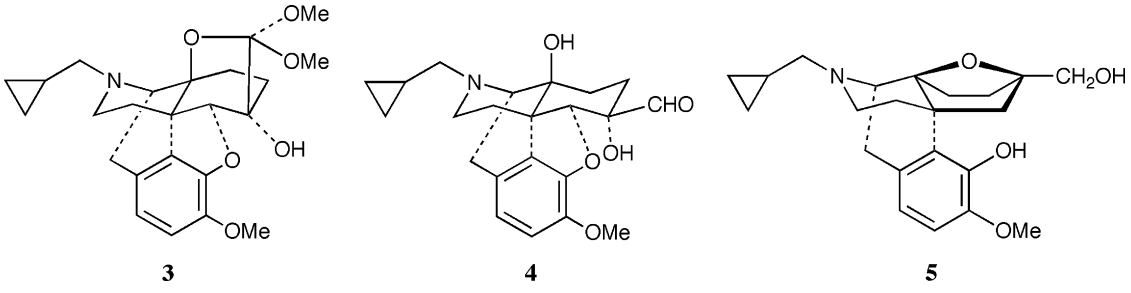
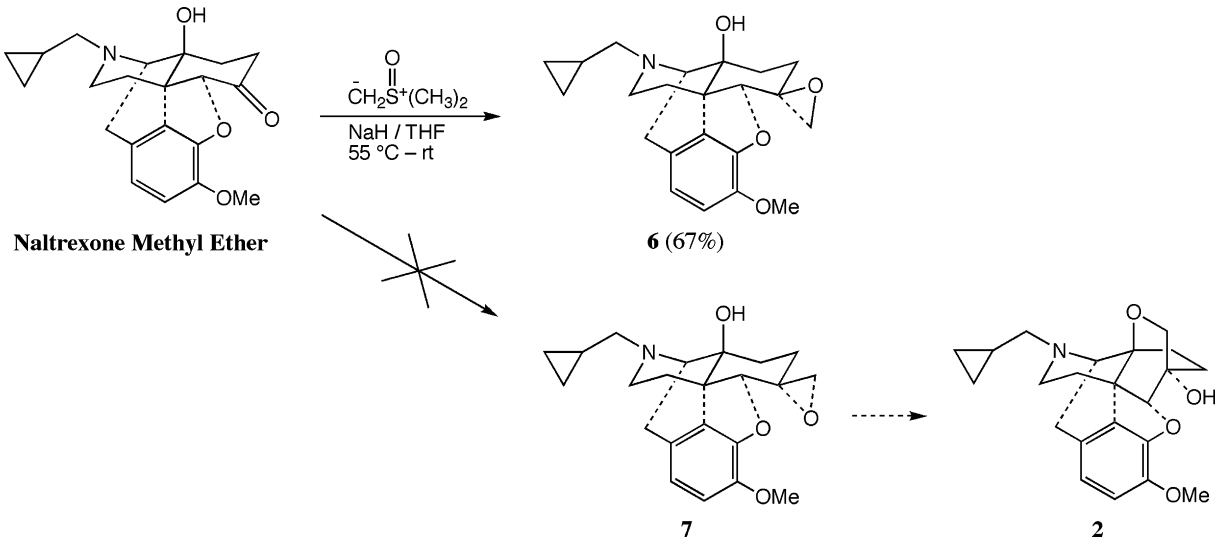


Figure 2.

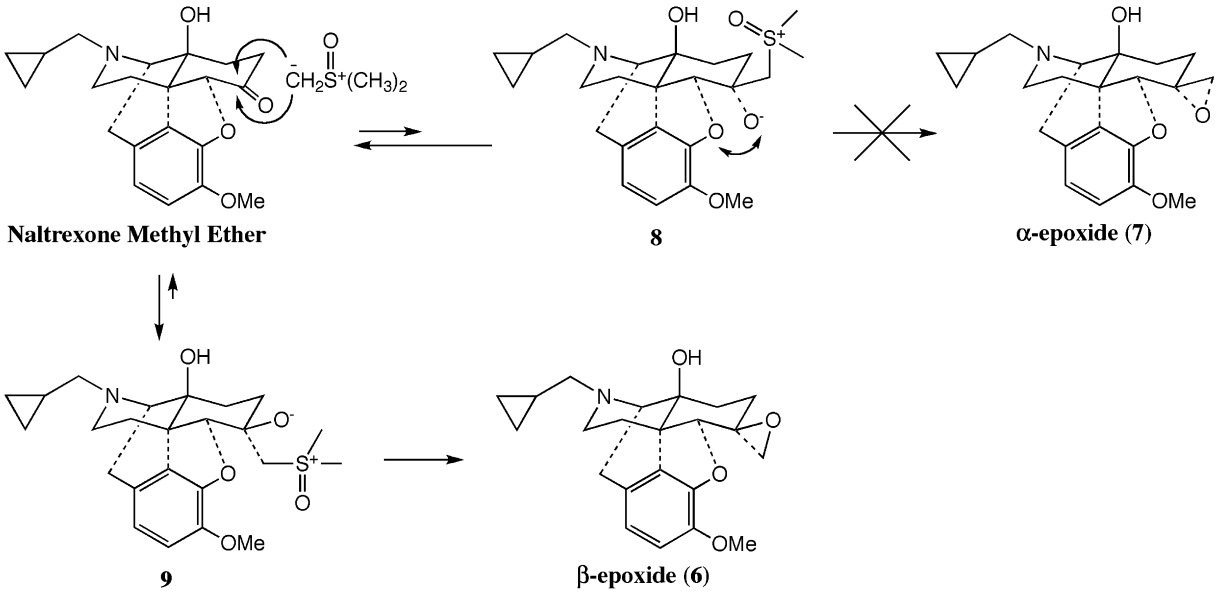
reaction of stable ylide to afford the resulting stable β alcohol (**9**) without the dipole–dipole interaction as shown in Scheme 2.

If this postulation was correct, 4,5-epoxy ring-opening compound (**10**)[7] could give the objective α epoxide (**11**) by the reaction with the stable ylide. Although compound (**10**) has a 4-hydroxy group without a 4,5-epoxy ring, it may be rather more flexible and the 4-hydroxy group could move to a position which could not participate in a dipole–dipole interaction with the α hydroxy group at 6 position. So α epoxide (**11**) will be expected to convert to the objective compound (**12**). However, surprisingly, when ring-opening compound (**10**) was treated with the stable ylide at 55 °C, an unexpected product (**5**) was obtained in 58% yield (Scheme 3).

The structure determination of compound (**5**) was examined by NMR and mass spectroscopy, and its stereochemistry was elucidated by ^{1}H NMR and NOE experiments.[8] NOE was observed between the methylene and C5-equatorial protons, and the methylene and C7-equatorial protons. Long-range coupling was also observed between the C5-equatorial and C7-equatorial protons ($J = 3.0$ Hz). In the HMBC spectrum of **5**, the proton signals at 3.86 ppm and 3.94 ppm (each methylene proton) showed a correlation with the carbon signals at 88.78 ppm (C6), respectively (Fig. 3).



Scheme 1.



Scheme 2.

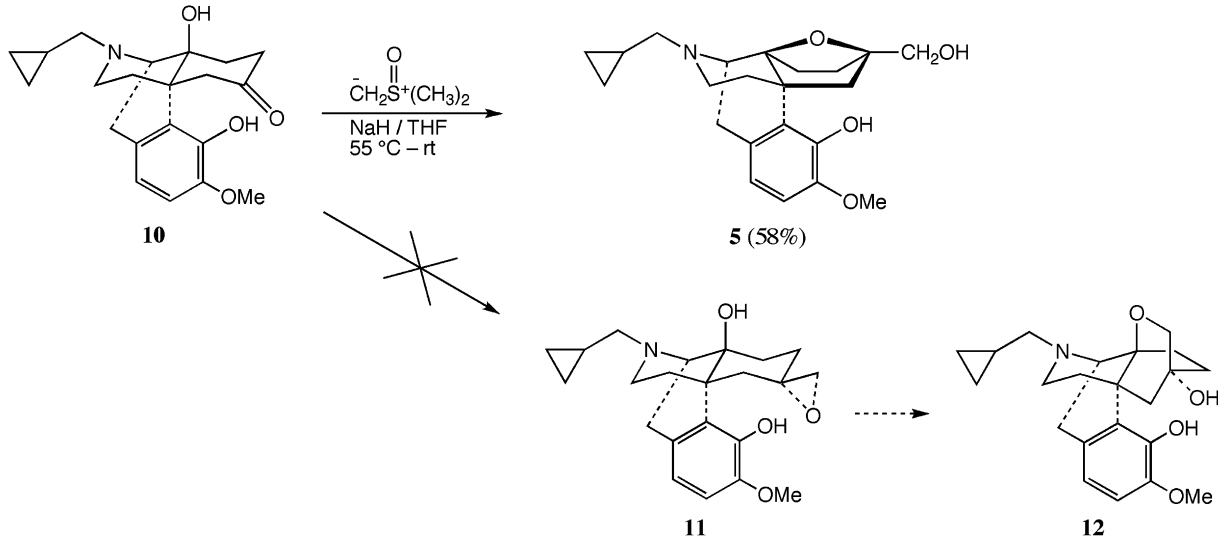
To investigate the source of the unexpected cyclization, a compound with oxabicyclo[2.2.1]heptane skeleton (**15**) was obtained from a precursor without a 4-hydroxy group (**13**),[7] employing the same stable ylide via α epoxide (**14**). The reaction of morphinan methyl ether (**13**) with the stable sulfur ylide derived from trimethylsulfoxonium iodide was effected at room temperature and the definitive intermediate, α epoxide (**14**), was isolated, and then treated with sodium hydride in DMF at 80 °C to afford objective bicyclic compound (**15**) (Scheme 4).

Cyclization of **14** may proceed via boat conformation. The distance between the 14-hydroxy group and the 6-quarternary carbon would be closer than the distance between the 14-hydroxy group and methylene carbon of the α epoxide, which might lead to the cyclization to afford **15** as shown in Scheme 5. On the other hand, Baldwin's rule could explain this selective cyclization.

This reaction was also conducted using the unstable ylide derived from trimethylsulfonium iodide to give α epoxide (**14**) in 65% yield, which was treated with sodium hydride in DMF at 80 °C to give the objective compound (**15**) (Scheme 6).

On the other hand, when naltrexone methyl ether was treated with the unstable ylide at 0 °C in THF–DMSO, initial objective product (**2**) was obtained in 62% concomitant with the methyl ether derivative (**16**) (Scheme 7).

The structure of **2** was confirmed by NMR, mass spectra, X-ray crystallographic analysis, and its stereochemistry



Scheme 3.

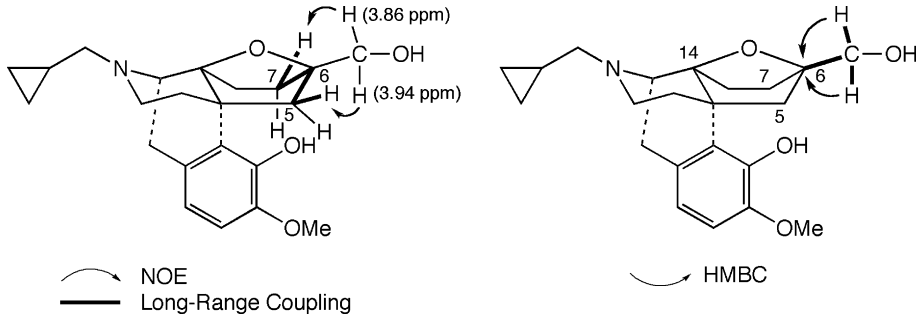
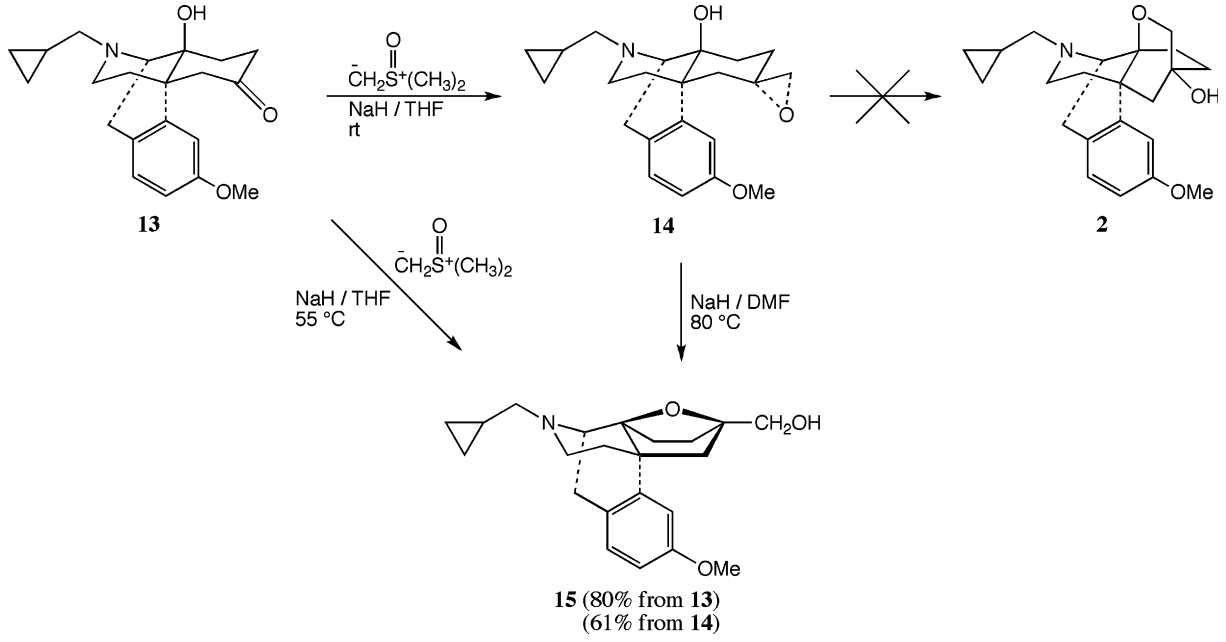
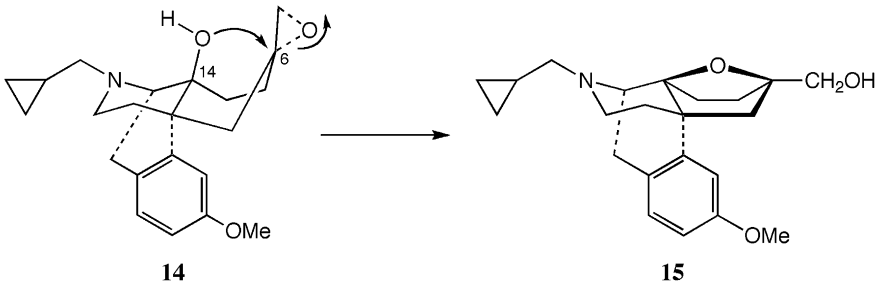


Figure 3.



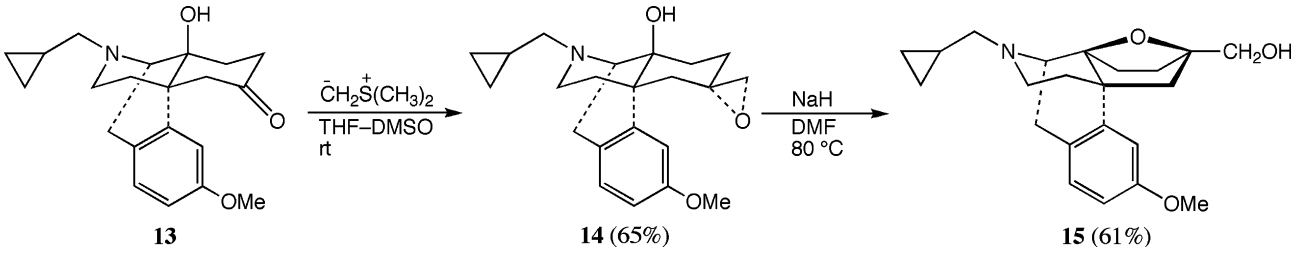
Scheme 4.

was elucidated by ^{1}H NMR spectrum.[9] Long-range coupling was observed between the 7- and 7′-axial protons ($J = 3.0$ Hz), and the 5- and 7′-equatorial protons ($J = 1.5$ Hz), respectively. In the HMBC spectrum of



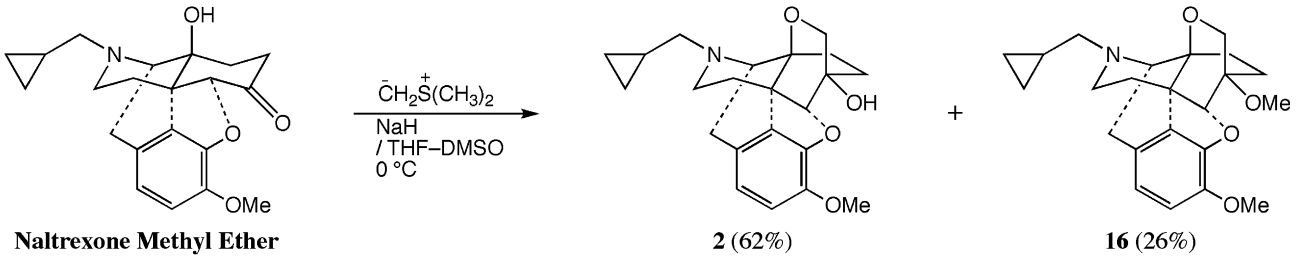
14 **15**

Scheme 5.



13 **14** (65%) **15** (61%)

Scheme 6.



Naltrexone Methyl Ether **2** (62%) **16** (26%)

Scheme 7.

2, the proton signals at both 3.78 ppm (C7–H) and 3.84 ppm (C7–H) showed a correlation with the carbon signals at 72.66 ppm (C14) (Fig. 4).

In this case, once this unstable ylide attacked from the β side of 6-ketone, this ylide cannot be displaced because of irreversible reaction, and the presence of the 4,5-epoxy ring may disturb formation of ideal boat form of the resulting compound (**14**), which may bring the 14-hydroxy group and the methylene group of the methyl sulfonium portion into closer proximity than the corresponding 6-carbon of **17** to give the oxabicyclo[2.2.2]octane skeleton (Scheme 8).

Demethylation of **2** using 1-propanethiol afforded **18** (Scheme 9).[10] The structure of **2** was also confirmed by the X-ray crystallographic analysis of **18** (Fig. 5).[11]

In summary, we successfully obtained two types of novel skeletons from morphinan and 4,5-epoxymorphinan

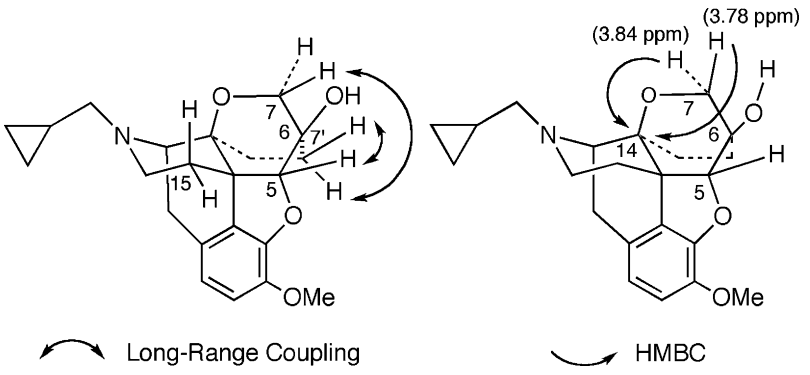
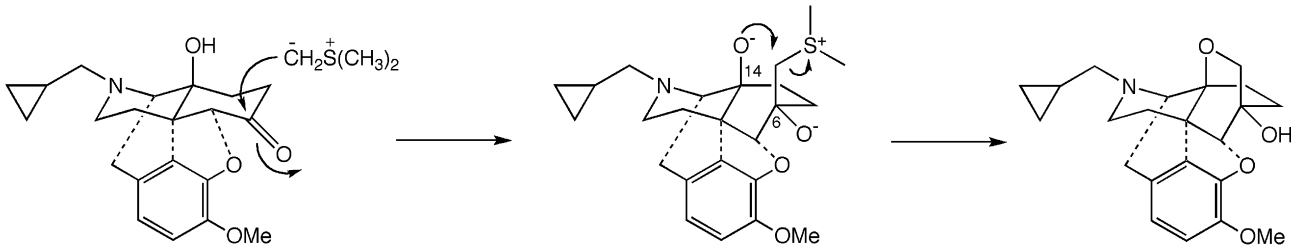
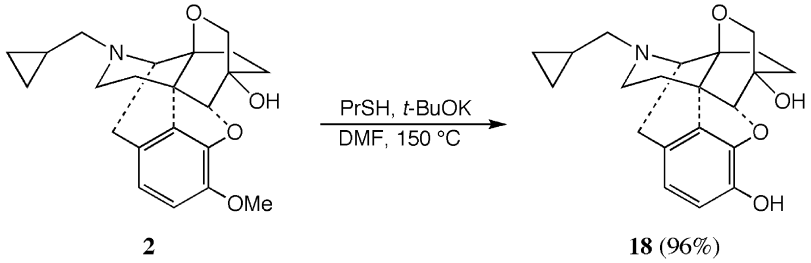


Figure 4.



Scheme 8.



Scheme 9.

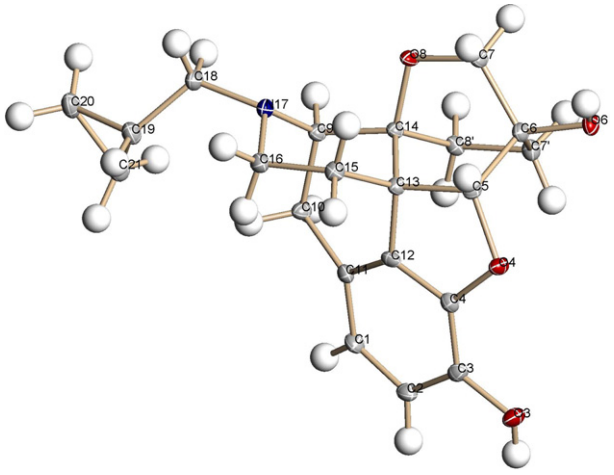


Figure 5.

derivatives by using stable and unstable sulfur ylides. The ring strain of the 4,5-epoxy ring led to oxabicyclo[2.2.2]octane skeleton by the reaction with unstable ylide, but not with the stable ylide. On the other hand, morphinan derivative without the 4,5-epoxy ring afforded the oxabicyclo[2.2.1]heptane skeleton independently by stability of the ylide.

Acknowledgements

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References and notes

1. Reisine, T.; Pasternak, G. In *Opioid Analgesics and Antagonists. Pharmaceutical Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. E., Ruddon, R. W., Gilman, A. G., Eds.; Mcgraw-Hill: New York, NY, 1995; pp 521–556.
2. Xu, J. Y.; Fujimoto, J. M.; Tseng, L. F. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 246–252.
3. Burkey, T. H.; Ehlert, F. J.; Hosohata, Y.; Quack, R. M.; Cowell, S.; Hosohata, K.; Varga, E.; Stropova, D.; Li, X.; Slate, C.; Nagase, H.; Porreca, F.; Hruby, V. J.; Roeske, W. R.; Yamamura, H. I. *Life Sci.* **1998**, *62*, 1531–1536.
4. Fujii, H.; Narita, M.; Mizoguchi, H.; Murachi, M.; Tanaka, T.; Kawai, K.; Tseng, L. F.; Nagase, H. *Bioorg. Med. Chem.* **2004**, *12*, 4133–4145.
5. Watanabe, A.; Kai, T.; Nagase, H. *Org. Lett.* **2006**, *8*, 523–526.
6. Trost, B. M.; Melvin, L. S. In *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975.
7. Sawa, Y. K.; Tada, H. *Tetrahedron* **1968**, *24*, 6185–6196.
8. *Analytical and spectral data for compound* **5**. IR (neat): 3376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.03–0.17 (m, 2H), 0.44–0.57 (m, 2H), 0.96 (m, 1H), 1.34 (ddd, 1H, $J = 3.0$, 9.0, 10.0 Hz), 1.51 (ddd, 1H, $J = 2.0$, 2.5, 13.0 Hz), 1.58 (dt, 1H, $J = 3.0$, 12.0 Hz), 1.75 (dddd, 1H, $J = 3.0$, 5.5, 10.0, 12.0 Hz), 1.88 (ddd, 1H, $J = 5.5$, 9.0, 12.0 Hz), 2.01 (dd, 1H, $J = 3.0$, 12.5 Hz), 2.04 (dt, 1H, $J = 2.5$, 13.0 Hz), 2.12 (d, 1H, $J = 12.5$ Hz), 2.16 (dt, 1H, $J = 4.5$, 13.0 Hz), 2.34 (m, 1H), 2.53 (m, 1H), 2.62 (ddd, 1H, $J = 2.0$, 4.5, 13.0 Hz), 2.66 (dd, 1H, $J = 6.0$, 18.0 Hz), 3.10 (d, 1H, $J = 18.0$ Hz), 3.65 (d, 1H, $J = 6.0$ Hz), 3.85 (s, 3H), 3.86 (d, 1H, $J = 12.5$ Hz), 3.94 (d, 1H, $J = 12.5$ Hz), 5.62 (s, 1H), 6.66 (d, 1H, $J = 8.0$ Hz); MS (EI) *m/z*: 371 $[M]^+$.
9. *Analytical and spectral data for compound* **2**. Mp 95–100 °C (recrystallized from methanol); IR (film): 3389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.01–0.11

(m, 2H), 0.38–0.58 (m, 2H), 0.77–0.96 (m, 2H), 1.41–1.77 (m, 4H), 2.11 (dd, 1H, $J = 7.0$, 12.0 Hz), 2.22 (dt, 1H, $J = 5.0$, 12.0 Hz), 2.26 (dd, 1H, $J = 6.0$, 18.0 Hz), 2.34 (dt, 1H, $J = 3.0$, 12.0 Hz), 2.61 (dd, 1H, $J = 5.0$, 12.0 Hz), 2.67 (dd, 1H, $J = 3.0$, 10.0 Hz), 3.14 (d, 1H, $J = 18.5$ Hz), 3.44 (d, 1H, $J = 6.5$ Hz), 3.78 (dd, 1H, $J = 3.0$, 9.0 Hz), 3.84 (s, 3H), 3.84 (d, 1H, $J = 9.0$ Hz), 4.42 (d, 1H, $J = 1.5$ Hz), 6.53 (d, 1H, $J = 8.0$ Hz), 6.68 (d, 1H, $J = 8.0$ Hz); MS (EI): m/z 369 $[M]^+$; HRMS (FAB): calcd for $C_{22}H_{28}NO_4$: m/z 370.2013 $[M+H]^+$. Found: 370.2020. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.69; H, 7.47; N, 3.86.

10. *Analytical and spectral data for compound* **18**. Mp 240–242 °C (recrystallized from ether); IR (KBr): 3276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.06–0.18 (m, 2H), 0.42–0.63 (m, 2H), 0.81–1.01 (m, 2H), 1.46–1.83 (m, 4H), 2.17 (dd, 1H, $J = 7.5$, 13.0 Hz), 2.21–2.47 (m, 3H), 2.69 (dd, 1H, $J = 5.0$, 12.0 Hz), 2.75 (dd, 1H, $J = 3.0$, 12.0 Hz), 3.17 (d, 1H, $J = 18.0$ Hz), 3.50 (d, 1H, $J = 6.5$ Hz), 3.84 (dd, 1H, $J = 2.5$, 9.5 Hz), 3.89 (d, 1H, $J = 9.5$ Hz), 3.89 (d, 1H, $J = 9.5$ Hz), 4.50 (d, 1H, $J = 1.0$ Hz), 6.52 (d, 1H, $J = 8.0$ Hz), 6.71 (d, 1H, $J = 8.0$ Hz); MS (FAB): m/z 356 $[M+H]^+$; HRMS (FAB): calcd for $C_{21}H_{26}NO_4$: m/z 356.1856 $[M+H]^+$. Found: 356.1860. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.86; H, 7.14; N, 3.96.
11. CCDC 630585 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.