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Regiospecific and Stereoselective Syntheses of (±) Morphine, Codeine, and Thebaine via a Highly Stereocontrolled Intramolecular 4 + 2 Cycloaddition Leading to a Phenanthrofuran System

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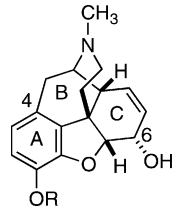
Abstract: Total syntheses of the morphine alkaloids are described that use a direct stereoselective formation of the phenanthrofuran system via an intramolecular 4 + 2 cycloaddition of a diene tethered to the 4-position of a 7-methoxybenzofuran-3-carboxylic acid ester.

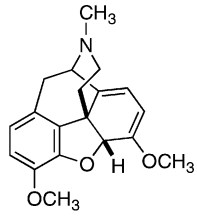
Introduction

Over half a century ago, the total synthesis of morphine was accomplished by Marshall Gates.[1a] A very large number of total syntheses of natural products have been carried out since that time, often with the goal of making medically significant natural substances more available. Efficiency was clearly a major concern. Frequently, however, the fascination of a synthesis target comes from the architectural challenges presented by an intricate structure, and originality of design is the goal.

In the case of the morphine alkaloids,[2] the specific structural challenge of having four rings sharing the same carbon atom is further complicated by their propensity to undergo sometimes spectacular rearrangements.[3] In any case, it is remarkable that numerous total syntheses of morphine (**1**) and/or its relatives, codeine (**2**), and thebaine (**3**), have been reported in the literature between the 1952 Gates synthesis and the latest publication in 2009.[1]



1 : R = H
2 : R = CH_3



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Our own interest in the synthesis of the morphine alkaloids[4] arose because the numerous approaches followed to their syntheses did not include the direct formation of the phenanthrofuran ring system of morphine by the intramolecular 4 + 2 cycloaddition of a diene tethered to the C-4 of a suitably substituted benzofuran ring.[5] Our work on that eventually successful approach is sketched in Figure 1.

Stereochemical Suitability of the Intramolecular Diels−Alder Route. Two questions arose as we considered such an intramolecular 4 + 2 cycloaddition. First, the nature of R, which eventually has to be transformed into an ethanamine chain connected to ring B. A carbomethoxy group appeared to be

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(1) (a) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109–1110. **1956**, *78*, 1380−1393. (b) Elad, D.; Ginsburg, D. *J. Am. Chem. Soc.* **1954**, *76*, 312–313. (c) Grewe, R.; Fischer, H. *Chem Ber.* **1963**, *96*, 1520–1528. (d) Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550–1558. (e) Barton, D. H. R.; Bhakuni, D. S.; James, R.; Kirby, G. W. *J. Chem. Soc. C* **1967**, 128–132. (f) Morrison, G. C.; Waite, R. O.; Shavel, J., Jr. *Tetrahedron Lett.* **1967**, *8*, 4055–4056. (g) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. C* **1969**, 2030–2033. (h) Schwartz, M. A.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239–1240. (i) Beyerman, H. C.; Lie, T. S.; Maat, M.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 24–25. Lie, T. S.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 419–420. (j) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135–3137. (k) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, 285–288. (l) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227–238. (m) White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron* **1983**, *39*, 2393–2397. (n) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473–475. *J. Org. Chem.* **1988**, *53*, 4694. (o) Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959–5966. (p) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688–9689; *J. Org. Chem.* **1994**, *59*, 3927−3933; *J. Org. Chem.* **2006**, *71*, 449−455. (q) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029. Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453–3456. (r) Mulzer, J.; Duerner, G.; Trauner, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2830–2832. Mulzer, J.; Bats, J. W.; List, B.; Opatz, T.; Trauner, D. *Synlett* **1997**, 441–444. Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908–5918. Mulzer, J.; Trauner, D. *Chirality* **1999**, *11*, 475–482. (s) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250–5251. *J. Org. Chem.* 1999, *64*, 7871−7884. (t) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* **2001**, 1094–1095. (u) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416–12417. (v) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803. (w) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311–5313. *Heterocycles* **2009**, *77*, 1219−1234. (x) Omori, A. T.; Finn, K. J.; Leisch, H.; Carroll, R. J; Hudlicky, T. *Synlett* **2007**, 2859–2862. (y) Verin, M.; Barré, E.; Iorga, B.; Guillou, C. *Chem.−Eur. J.* **2008**, *14*, 6606–6608. (z) Tanimoto, H.; Saito, R.; Chida, H. *Tetrahedron Lett.* **2008**, *49*, 358–362.

10.1021/ja9038505 CCC: $40.75

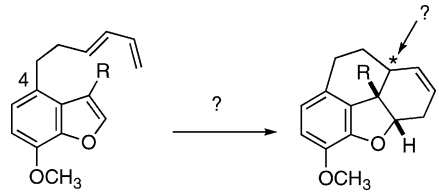
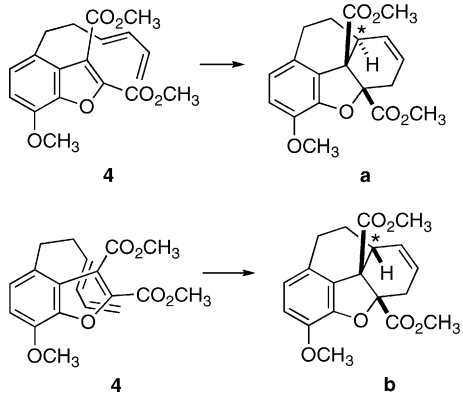
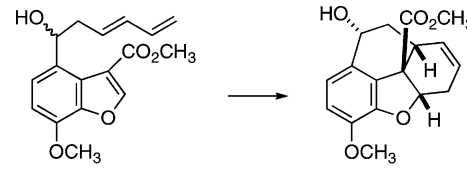


Figure 1

suitable for that eventual transformation, and should facilitate the planned cycloaddition. Most important was whether the addition would take place with the diene endo to the ester, leading to adduct **a**, with the *unwanted* relative stereochemistry at the starred center, or exo to it (an addition probably more relevantly described as endo to the benzofuran), *thus leading to the desired outcome* shown in **b**.



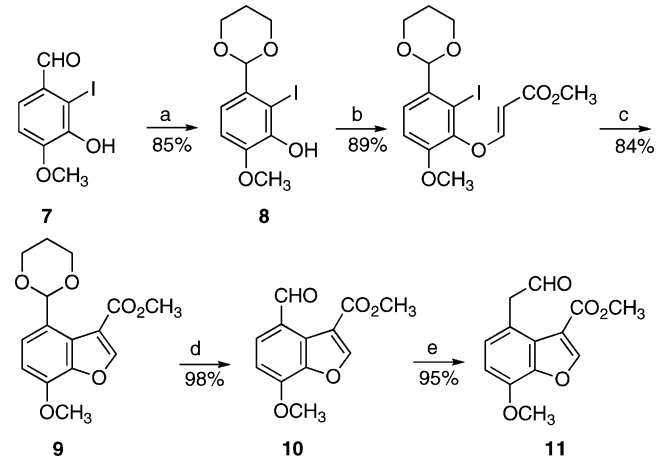
Early experiments in our laboratory were actually performed with the benzofuran *d*iester **4**, and showed (X-ray)[6] that the adduct isolated from **4** was the *desirable* isomer **b** above. This favorable result led us, eventually, to examine whether the methoxycarbonyl at C-2 (which would eventually have to be removed) was required for the subsequent 4 + 2 cycloaddition and, if not, whether one would still get an endo to benzofuran cycloaddition. We selected the 3-carbomethoxybenzofuran derivative **5**[7] to explore these questions, and were pleased to find that, here again, 2 + 4 cycloaddition had followed the path that led to **b** and producing structure **6** (established by X-ray of its acetate; cf Supporting Information) with the resulting correct relative arrangement of the three contiguous centers in ring C.



The favorable result just described suggested that one could easily complete a formal synthesis of the morphine alkaloids from adduct **6**. This would require straightforward transformation of the carbomethoxy group to an *N*-tosylethanamine chain, followed by its attachment to ring B, after dehydration to a styrene system, by application of the Parker piperidine ring closure.[1p] We successfully carried out these and other necessary transformations to (±) codeine, but we will describe fully here a less predictable route in which the starting diene system is introduced into benzofuran*acetadehyde* **11**. This variation was made in the hope that eventual closure of the piperidine ring could be simply achieved by dispacement of a derivative of the secondary carbinol in ring B of the adduct (cf. Scheme 1).

The synthesis of **11** is outlined in Scheme 1. It starts with the acetal **8** of the readily available iodoisovanillin **7**.[8] Conjugate addition of **8** to either methyl propiolate or methyl 3-chloroacrylate gave what proved to be a suitable precursor of the desired

Scheme 1[a]



[a] Conditions: (a) $HO(CH_2)_3OH$, p-TSOH, toluene; (b) methyl propiolate; Et_3N, THF; (c) $Pd(OAc)_2$, Ph_3P, NaOAc, *n*-Bu_4NCl, DMF, 125°; (d) HCl, THF; (e) (1) $Ph_3PCH_2OCH_3Cl$, KHMDS, THF, (2) HCl, THF.

(2) For several excellent recent reviews related to morphine (biological action, biogenesis, total syntheses, and various approaches, see, inter alia: Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159–1168. Taber, D. F.; Neubert, T. D.; Schlecht, M. F. in *Strategies and Tactics in Organic Synthesis*; Harnata, M., Ed.; Elsevier: London, 2004, Vol. 5, pp 353−389. Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388–405. Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007, pp 726−757.

(3) "The star performers in the team of molecular acrobats are undoubtedly the alkaloids of the morphine group." Robinson, R. *Proc. R. Soc. London* **1947**, *B135*, xiv.

(4) Starting with early unsuccessful synthesis attempts: Stork, G.; Conroy, H. *J. Am. Chem. Soc.* **1951**, *73*, 4748–4751. See also: Stork, G. in *The Alkaloids*; Manske, R. H. F.; Holmes, H. L., Eds.; Academic Press: New York, 1952; Vol. II, Chapter 8, Part II, pp 171−203; Stork, G. *The Alkaloids*; Vol. VI, chapter 7, pp 219−245.

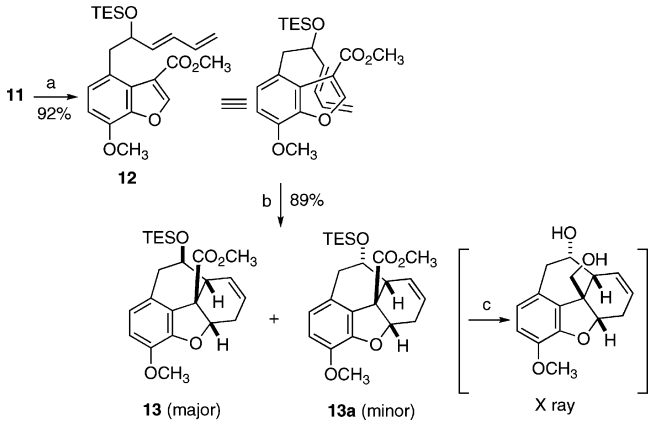
(5) For *inter*molecular additions to benzofurans, see: Wenkert, E.; Piettre, S. R. *J. Org. Chem.* **1988**, *53*, 5850–5853, For *intra*molecular, B-*seco* morphine related, 4 + 2 additions to benzofurans, see. (a) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261–6262. (b) France, S.; Boonsombat, J.; Leverett, C. A.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 8120–8123. The possibility of a direct formation of a phenanthrofuran system via an intramolecular Diels Alder was considered by Parsons, P. J. *Chem. Rev.* **1996**, *96*, 197. For different approaches to phenanthrofuran precursors of morphine alkaloids, see inter alia: Fuchs, P. M. (ref 1n). Parker, K. A. (ref 1p).

(6) Carried out in 1982 by Ms. Gayle Schulte in Professor Jon Clardy's Laboratory at Cornell University.

(7) Experimental details of the synthesis of 1,3-pentadienecarbinol **5** from the benzofurancarboxaldehyde **10** are described in the Supporting Information, as is the X-ray of the acetate of Diels−Alder adduct **6**. That X-ray showed that selective formation of a specific diastereomer of the secondary hydroxyl in ring B of **6** had taken place. This is potentially useful because, even though that hydroxyl would have to be removed at some future point, it means that one could select the correct enantiomer of starting carbinol **5** to produce either enantiomer of the synthetic alkaloid. We did not take advantage of that possibility because enantioinduction was not a goal of our work. The synthetic substances synthesized in this work are racemic: the structural drawings in this work indicate their relative stereochemistry.

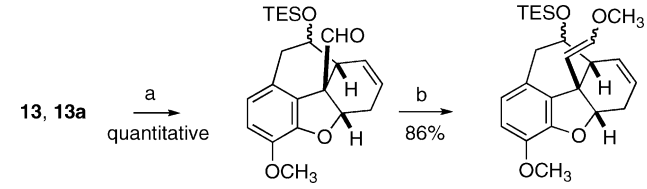
(8) Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. Y.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992**, *35*, 466–479.

Scheme 2[a]



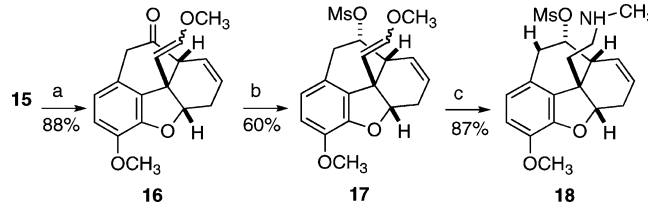
[a] Conditions: (a) (1) 3-Buten-1-yne, $ZrCp_2(H)Cl$, AgOTf, CH_2Cl_2, (2) TESCl, imidazole. (b) Decalin, Et_3N, 230 °C. (c) (1) TBAF, THF, (2) super hydride, CH_2Cl_2.

Scheme 3[a]



[a] Conditions: (a) (1) Super-hydride, THF, (2) Dess−Martin, CH_2Cl_2. (b) $Ph_3PCH_2OCH_3Cl$, KHMDS, CH_2Cl_2−THF.

Scheme 4[a]



[a] Conditions: (a) (1) TBAF, THF, (2) Dess−Martin, CH_2Cl_2, 0°. (b) (1) L-Selectride, THF, 0°, (2) MsCl, Et_3N, CH_2Cl_2, 0°. (c) (1) HCl, THF, (2) $MeNH_2 \cdot HCl$, Et_3N, $Ti(OiPr)_4$, MeOH, (3) $NaBH_4$.

benzofuran-3-carboxylic acid derivative **9**, via a Heck reaction catalyzed by palladium acetate.[9] Dilute acid hydrolysis of the acetal, followed by homologation by the usual Wittig−Levine reaction,[10] now gave the desired benzofuranacetaldehyde **11**.

Intramolecular 4 + 2 Cycloaddition. Our initial target was the TES-protected dienyl carbinol **12**. Participation of the butadiene system of **12** in a Diels−Alder addition requires that the disubstituted allylic double bond has the (**E**) stereochemistry shown: the Suzuki process[11] was selected as a particularly effective method of achieving that result. Hydrozirconation of vinylacetylene with the Schwartz reagent,[12] followed by in situ reaction of the (E) vinylzirconium intermediate with benzofuranacetaldehyde **11,** and trapping with chlorotriethylsilane gave the desired **12** in excellent yield (Scheme 2).

Considerable experimentation was involved in determining the conditions that were eventually selected for the cycloaddition: degassed decalin solution heated for 5 h, under argon, at ∼230 °C (bath temperature) in a sealed pressure flask, in the presence of some triethylamine. Under those conditions, phenanthrofurans **13** and **13a** (89% yield in a 4/1 ratio) were obtained. *The structure of the desilylated minor isomer* **13a**, *was established by X-ray crystallography* (cf Supporting Information). That of the major isomer **13** was tentatively written as shown because it readily formed a lactone on desilylation, and because we assumed (correctly, as it turned out) that it, like **13a**, again came from the now familiar *endo benzofuran* transition state. The formation of **13** as the major adduct further implies that, in the 4 + 2 cycloaddition leading to it, the benzofuran and the OTES group are positioned so they end mostly cis to each other.[13]

If the relationship of the asymmetric centers in **13** is as that in **13a**, then they both would have the required all cis arrangement of the three crucial contiguous centers around ring C. Obviously, however, the protected hydroxyl of **13** would have to be inverted to that of minor isomer **13a** to take part in the closure planned for the piperidine ring. Fortunately, however, the *mixture* of epimers **13** and **13a** could be used without separation because both should converge to the same ketone (±)**16**.[14] As the sequel shows, this proved to be the case.

Elaboration of the Ethanamine Chain. Construction of the piperidine ring of the opium alkaloids has been carried out following a variety of pathways, but, surprisingly, not by a simple intramolecular *displacement* involving an ethanamine chain. This presents an interesting challenge here, because the basicity of the ethanamine chain suggests competition between the desired displacement process and a base-catalyzed elimination.

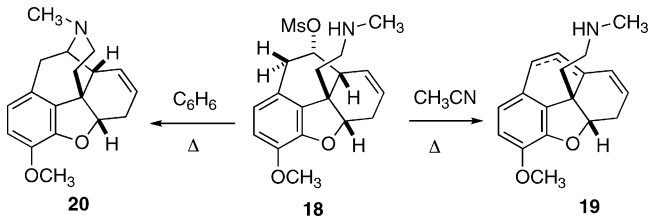
Conversion of the ester group in **13**,**13a** to an ethanamine was carried out by standard operations (cf Scheme 3), to produce enol ethers **15** of the precursor acetaldehyde chain.

The assumption that both **13** and **13a** would lead to the same ketone (**16**) was verified,[14] and as anticipated from its shape, reduction with L-Selectride (Scheme 4) took place from the more accessible face and gave the α-hydroxyl stereochemistry required for the formation of mesylate **17**. The ethanamine chain needed for the planned cyclization was now established by hydrolysis of the methyl enol ether in **17**, followed by reaction of the resulting aldehyde with methylamine in the presence of titanium tetraisopropoxide, and in situ reduction of the resulting imine with sodium borohydride.[15] Methylaminomesylate **18**, thus obtained in 87% yield from **17**, was ready for the crucial issue of displacement versus elimination. This was anticipated to be a serious problem because, in **18**, the relevant hydrogens adjacent to the mesylate can attain antiperiplanar arrangement with it, and they are readily reached by the methylamine group, thus leading to unwanted arylethylene or conjugated diene.

(±) **Deoxycodeine.** There have been a large number of experiments and discussions in the literature about the competi-

(9) For a related case, cf: Henke, B. R. et al *J. Med. Chem.* **1997**, *40*, 2706−2725.
(10) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151.
(11) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 1557–1564. Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965–5968. Maeta, H.; Suzuki, K. *Tetrahedron Lett.* **1993**, *34*, 341–344.
(12) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340.
(13) Possibly as a result of attraction between the carbonyl of the ester and the OTES group.
(14) Actually, because the enol ether system precursor of the acetaldehyde chain is itself an (operationally irrelevant) *E*/*Z* mixture, convergence to a single ketone was cleanly observable only after hydrolysis of enol ether **17** to the related aldehyde.
(15) (a) Mattson, R.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552–2554. (b) Neidigh, K. A.; Avery, M. A.; Williams, J. S.; Bhattacharyya, S. J. *J. Chem. Soc. Perkin Trans. I* **1998**, 2527–2532.

Scheme 5



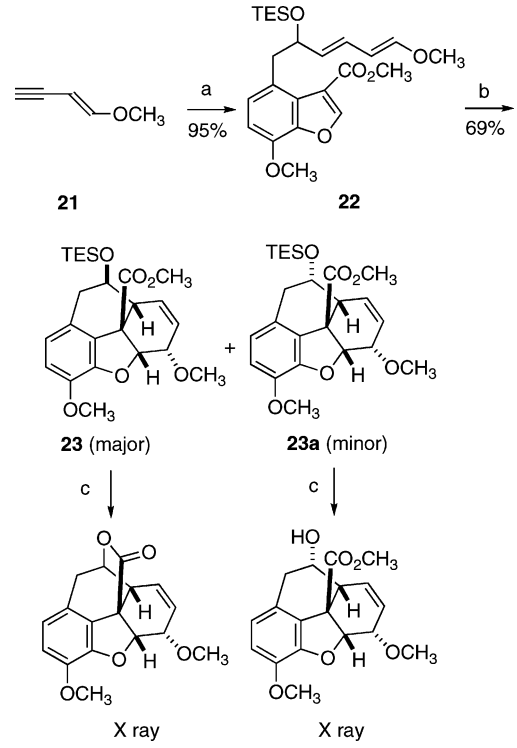
tion between SN2 displacements and E2 eliminations, particularly in simple β-phenethyl systems. The aminomesylate **18** involves a similar competition, although, in our case, both pathways are intramolecular.

While the existing evidence may not be applicable to our case, it strongly suggests that a departing sulfonate favors substitution compared with a bromide or iodide.[16] We were, nevertheless, unprepared to find (Scheme 5) that, in refluxing acetonitrile, essentially complete elimination of mesylate **18** (cf, **19**) was observed. Fortunately, in benzene solution at 75 °C for 24 h, displacement took place,[17] with the formation of (±) 6-deoxycodeine (**20**), in 53% yield, accompanied by ~30% elimination. A possible interpretation of these observations is that there may be, at least in this particular case, more charge separation in the transition state for the elimination reaction than in that for the desired substitution. Additional factors are likely to be involved (conformational?) because in the presence of a methoxyl at C-6 (in our precursor of codeine methyl ether, *vide infra*), the similar reaction in benzene appears to lead to the desired substitution *with significantly less elimination*.

The above construction of (±) 6-deoxycodeine may be claimed to constitute a formal synthesis of (±) codeine because we found it possible to introduce the missing oxygen at C-6 via selenium dioxide oxidation of the *N*-methylcarbamate derived from our (±) 6-deoxycodeine to the corresponding N-derivative of *iso*codeine in 61% yield.[18] The transformation of isocodeine into codeine[19] (and the latter into morphine[20]) is well-known. It was, however, thought interesting to examine whether the eventually required oxygen at C-6 might be introduced at a much earlier stage, as a terminal substituent on the conjugated diene of **12**. This approach, starting with a methoxydiene addition to benzofuran **11**, was successful. It allowed a synthesis of both thebaine (**3**) and codeine (**2**) from an intermediate codeine methyl ether. This is described below.

Codeine Methyl Ether and Thebaine. Realization of the scheme just mentioned required the synthesis of 4-methoxy-3-butene-1-yne, more specifically of its 3,4 (E) isomer **21** (Scheme 6). As it happens, the 3,4 (Z) isomer is the one commercially available, but the required (E) isomer is known to be the major product of the reaction of the dimethyl ether of 2-butyne-1,4-

Scheme 6[a]



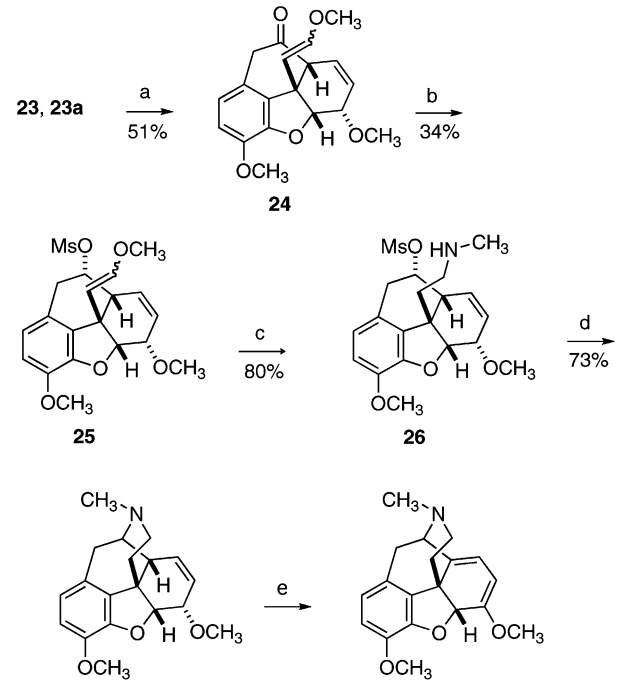
[a] Conditions: (a) (1) 11, $ZrCp_2(H)Cl$, AgOTf, CH_2Cl_2, (2) TESCl, imidazole. (b) Decalin, Et_3N, 240°, 24 h. (c) TBAF, THF.

diol with sodamide in liquid ammonia.[21] The small amount of (Z) isomer formed simultaneously can be readily separated, but this is unnecessary because it is expected to be much less reactive than the (E) isomer in the subsequent 4 + 2 cycloaddition. The Suzuki reaction sequence,[11] involving hydrozirconation and in situ addition to the benzofuranacetaldehyde **11**, proceeded, again in excellent yield, to the anticipated methoxydienyl carbinol, isolated as its TES derivative **22**, precursor of the planned 4 + 2 cycloaddition (Scheme 7). The 4 + 2 cycloaddition once more took place in the required "*endo-benzofuran*" mode, thus leading to the *correct relative stereochemistry of the five contiguous asymmetric centers shown in* **23**. Possibly as a result of some steric interference by the methoxy substituent on the "*endo benzofuran*" transition state, cycloaddition appeared to be slower than in the previous desmethoxy case: 24 h in benzene at 235−240 °C (bath temperature) gave 21% recovered starting material, in addition to 69% of a mixture (again 4:1) of a major and a minor adduct: X-ray structure determinations (see Supporting Information) of the crystalline alcohol obtained by removal of the TES protecting group of the minor adduct **23a** and of the crystalline lactone from **23** established that cycloaddition of **22** had proceeded, similarly to the previously described desmethoxy case, to give a 4:1 ratio of **23** to **23a** in favor of **23**.

As in the desmethoxy series, the ~4:1 mixture of isomeric TES-protected alcohols **23**, **23a** did not require separation because both proceed to the same (±)ketone **24** (Scheme 7). Following the procedures described earlier in the deoxycodeine synthesis, DIBAL reduction and mesylation to **25**, followed by

(16) Veeravagu, P.; Arnold, R. T.; Eigenmann, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 3072–3075.
(17) For an early example of an uneventful *intermolecular* displacement of the *primary halide* in 2-bromoethylbenzene by a secondary amine, in benzene, see: Foreman, E. L.; McElvain, S. M. *J. Am. Chem. Soc.* **1940**, *62*, 1435–1438.
(18) As described in the Supporting Information, the 61% yield in that oxidation with *tert*-butyl hydroperoxide/selenium dioxide in methylene dichloride was obtained only in the presence of a small amount of water. The observed regiochemistry may reflect the smaller structural distortion required for that transition state over the alternative. See also ref 1v.
(19) (a) Ijima, I.; Rice, K. C.; Silverton, J. V. **1977**, *6*, 1157–1165 (same process, but starting with the corresponding *ethyl* carbamate). (b) Schwartz, M. A.; Pham, P. T. K. *J. Org. Chem.* **1988**, *53*, 2318–2322.
(20) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164–165.
(21) Brandsma, L. *Preparative Acetylene Chemistry*; Elsevier: Amsterdam, 1971; p 181; Adams, H.; Anderson, J. C.; Bell, R.; Jones, D. N.; Peel, M. R.; Tomkinson, N. C. O. *J. Chem. Soc., Perkin Trans. I* **1998**, 3967–3974.

Scheme 7[a]



[a] Conditions: (a) (1) Super-hydride, THF, (2) Dess−Martin, CH_2Cl_2, (3) $Ph_3PCH_2OCH_3Cl$, KHMDS, CH_2Cl_2−THF, (4) TBAF, THF, (5) Dess−Martin, CH_2Cl_2, 0°. (b) (1) L-Selectride, THF, 0°, (2) MsCl, Et_3N, CH_2Cl_2, 0°. (c) (1) HCl, THF, (2) $MeNH_2 \cdot HCl$, Et_3N, $Ti(OiPr)_4$, MeOH, (3) $NaBH_4$. (d) K_2CO_3, benzene, 75°, 24 h. (e) Reference 22.

conversion of the enol ether side chain of **25** into the ethanamine chain, led to **26**, the precursor of the piperidine ring.

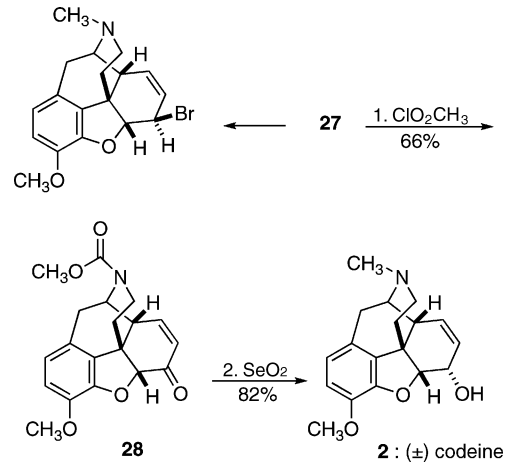
Intramolecular closure of the basic methylaminoethyl chain of **26** by displacement of the mesylate now involved the possible effect of the 6-methoxyl on the cyclization/elimination ratio from **26**. We were pleasantly surprised that in refluxing benzene, under the conditions used in the desmethoxy series (24 h in benzene, at 75 °C bath temperature) **26** gave (±) codeine methyl ether **27** in 73% yield.

(±) Thebaine. The specific formation of (±) codeine methyl ether just described permits that of (±) thebaine in just one additional step because the C-6 configuration of the (±) methyl ether of codeine (and not that of (±) isocodeine) can take advantage of the easy oxidation of the former to thebaine by manganese dioxide described many years ago by Barber and Rapoport[22] who also reported that, by contrast, the epimeric methyl ether of isocodeine was unchanged under their oxidation conditions.

Codeine from Codeine Methyl Ether. The completion of our synthetic project now required cleavage of the allylic methyl ether of **27** either directly to codeine, or to codeinone, since the reduction of codeinone, or its des*N*-methyl *N*-carbamate (cf **28**) to codeine is well-known,[19] involving simple hydride addition to the accessible face of the codeinone molecule simultaneously with the reduction of the carbamate.

This proved to be more of a problem than we had anticipated. Cleavage of the methyl ether proceeded very readily, and selectively, with boron tribromide, but the allylic

Scheme 8



nature of the methoxy group led to only a minor amount of codeine. The major cleavage, when the reaction was run for a very short time, was the 6-β-bromo compound. Steric hindrance on the underside (α) side of the molecule precluded simple inversion displacement, as by acetate. A number of exotic possibilities, such as two sequential S_N2' reactions, were explored with only limited success. We eventually recognized that the conformation factors involved (vide supra) in the formation of thebaine from codeine methyl ether with manganese dioxide,[22] and with the selenium dioxide oxidation of deoxycodeine (vide supra) might well allow *direct selenium dioxide oxidation of codeine methyl ether* to *codeinone*. This was successful. After quantitative transformation of **27** to its methyl carbamate by reaction with methyl chloroformate, selenium dioxide accomplished, in 72% yield, the hoped-for conversion into the carbamate of codeinone (**28**) (Scheme 8). The latter, as previously described,[19] underwent simultaneous reduction of the ketone carbonyl to the correct 6-hydroxyl stereochemistry, as well as of the urethane to regenerate the *N*-methyl group, thus producing the desired (±) codeine (**2**). Its spectral properties (NMR, IR, ESI−LCMS) matched those of natural (−) codeine.

Conversion of codeine to morphine (**1**) by cleavage of the aromatic methoxy group to the free phenol is known, both in the natural[20] and the (±)[1w] series: The 4 + 2 route to codeine, morphine, and thebaine was now complete.

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Supporting Information Available: Complete ref 9; experimental procedures and spectral data for all compounds from **5** onward. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9038505

(22) Barber, R. B.; Rapoport, H. J. *J. Med. Chem.* **1975**, *18*, 1074–1077.