Nucleophilic Alkylation on Anti-Bredt Iminium Ions. Facile Entry to the Synthesis of 1-Alkylated 2-Azabicyclo[3.3.1]nonanes (Morphans) and 5-Azatricyclo[6.3.1.0^{1,5}]dodecane

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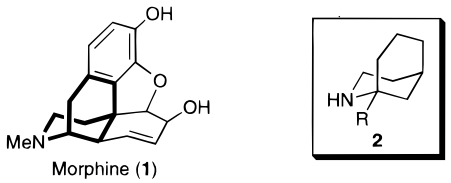
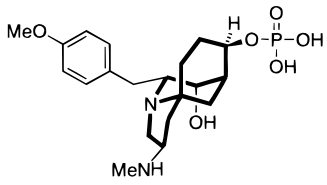
The 2-azabicyclo[3.3.1]nonane (morphan) ring system **2** (R = H) is present in morphine (**1**) and related synthetic compounds with analgesic activity such as levorphanol and pentazocine and also found in a great number of indole alkaloids.[1] Very recently, the discovery and structural determination of the novel immunosupressant FR901483 (**3**), isolated from the fermentation broth of *Cladobotryum* sp. No. 11231, was reported by the Fujisawa group.[2] From a structural point of view, the most

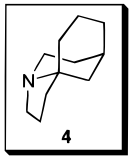


Morphine (**1**)

2



FR901483 (**3**)



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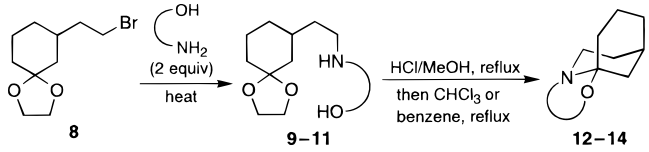
conspicuous feature of **3** is an azatricyclic ring system (shown by bold lines in **3**) consisting of the combination of the morphan and indolizidine nuclei sharing the piperidine ring, namely, 5-azatricyclo[6.3.1.0^{1,5}]dodecane (**4**). To our knowledge, such a unique ring system as well as the structural feature of the morphan framework with an alkyl substitution at the C-1 bridgehead position, with the exception of only a single example[3] for the latter case, are not otherwise present in known natural and synthetic compounds. Our interest in the synthetic study of **3** led us to develop a facile, general formation of the morphans possessing 1-alkyl substituents, i.e., **2**, wherein R = alkyl, and the construction of the 5-azatricyclo[6.3.1.0^{1,5}]dodecane core structure **4**.

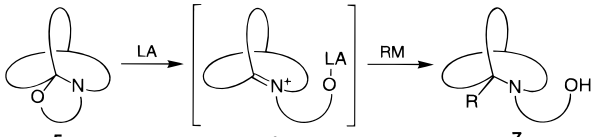
We have recently been investigating[4] the highly selective Lewis acid-induced nucleophilic alkylation with

Scheme 1



8 **9–11** **12–14**

organometallic reagents on hydrazine *N*,*O*-acetals. From these results it was envisioned, as outlined in eq 1, that



5 (LA = Lewis acid) **6** **7** (1)

using appropriate tricyclic *N*,*O*-acetals **5** such alkylation protocol could provide a new method for the alkylation of the bridgehead position proceeding by a pathway involving an S_N1 reaction on intermediary bridgehead iminium ions **6** with the carbon placed at the bridgehead. Despite Bredt's rule,[5] a variety of synthetic methods for the preparation of bridgehead carbocyclic olefins have been developed;[6] however, relatively few methods for anti-Bredt imines have appeared.[6c,7] In most cases, anti-Bredt imines have been generated by thermal and photochemical decomposition of bridgehead azides;[8] however, these methods are often complicated by the mixture of rearranged isomers of bridgehead imines. Alternatively, a few approaches involving $Pb(OAc)_4$ oxidation of an appropriate lactam[9] and an intramolecular aza-Wittig reaction[10] have been appeared. Although nucleophilic addition to these bridgehead imines with alcohols and cyanide ion has been frequently carried out in trapping experiments, no synthetic utilization with bridgehead imines has been explored. Herein, we report the first success in a facile, general entry to C−C bond formation at bridgehead iminium ions and application in the construction of 5-azatricyclo[6.3.1.0^{1,5}]dodecane (**4**).

The requisite tricyclic *N*,*O*-acetals **12**−**14** used in the study were prepared as outlined in Scheme 1. Condensation of 3-(2-bromoethyl)cyclohexanone ethylene ketal (**8**)[11] with 2-aminoethanol, 2-hydroxybenzylamine, and 2-(aminomethyl)benzyl alcohol (2 equiv were used in each case) at heating with or without a solvent gave the corresponding hydroxy amines **9**−**11**. Deketalization with HCl−MeOH (reflux) followed by heating in refluxing $CHCl_3$ or benzene resulted in the formation of the

(1) For a review of the synthesis of 2-azabicyclo[3.3.1]nonanes, see: Bosch, J.; Bonjoch, J. *Heterocycles* **1980**, *14*, 505.
(2) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.
(3) Cronyn, M. W.; Riesser, G. H. *J. Am. Chem. Soc.* **1953**, *75*, 1664.
(4) (a) Yamazaki, N.; Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 6161. (b) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623.
(5) (a) Fawcett, F. S. *Chem. Rev. (Washington D.C.)* **1950**, *47*, 219. (b) Wiseman, J. R.; Pletcher, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 956. (c) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 464. (d) Buchnan, G. L. *Chem. Soc. Rev.* **1974**, *3*, 41. (e) Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.
(6) For bridgehead olefin reviews, see: (a) Keese, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 528. (b) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (c) Warner, P. M. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1067. (d) Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1591. (e) Broden, W. T. *Tetrahedron* **1989**, *89*, 1095.
(7) For a review of synthesis of azaadamantanes via bridgehead imines, see: Eguchi, S.; Okano, T.; Takeuchi, H. *Heterocycles* **1987**, *26*, 3265.
(8) See, for example: (a) Sasaki, T.; Eguchi, S.; Katada, T.; Hiroaki, O. *J. Org. Chem.* **1977**, *42*, 3741. (b) Quast, H.; Eckert, P.; Seiferling, B.; Peters, E.-M.; Perters, K.; von Schnering, H. G. *Chem. Ber.* **1985**, *118*, 3058. (c) Quast, H.; Eckert, P.; Seiferling, B. *Chem. Ber.* **1985**, *118*, 3535. (d) Radziszewski, J. G.; Downing, J. W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799. (e) Wayne, G. S.; Snyder, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 9860. See also ref 7.
(9) Toda, M.; Niwa, H.; Ienaga, K.; Hirata, Y. *Tetrahedron Lett.* **1972**, 335.
(10) Sasaki, T.; Eguchi, S.; Okano, T. *J. Am. Chem. Soc.* **1983**, *105*, 5912.
(11) Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216.

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Table 1. Nucleophilic Alkylation with Organometallic Reagents on Cyclic *N,O*-Acetals 12−14

				product	
entry[a]	substrate	RM	method[b]	structure	yield, %[c]
1		Et_3Al	A	**15a**, R = Et	75
2		CH_2=$CHCH_2MgBr$	B	**15b**, R = CH_2CH=CH_2	trace
3		CH_2=$CHCH_2MgBr$	C	**15b**, R = CH_2CH=CH_2	84
4		EtMgBr	C	**15a**, R = Et	75
5	**12**	BnMgCl	C	**15c**, R = Bn	79
6		Et_3Al	A	**16a**, R = Et	82
7		CH_2=$CHCH_2MgBr$	C	**16b**, R = CH_2CH=CH_2	91
8		BnMgBr	C	**16c**, R = Bn	85
	13				
9		Et_3Al	A	**17a**, R = Et	73
10		EtMgBr	C	**17a**, R = Et	78
11		CH_2=$CHCH_2MgBr$	C	**17b**, R = CH_2CH=CH_2	86
12		BnMgBr	C	**17c**, R = Bn	92
	14				

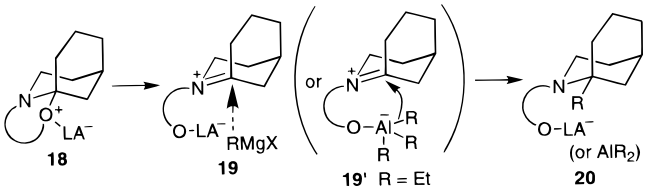
[a] All reactions were carried out at a substrate concentration of 0.2 M. [b] A: A mixture of the substrate and Et_3Al (2.5 equiv) in $CHCl_3$ was stirred at 0 °C for 5 min then at room temperature for 30 min. B: A mixture of the substrate and the Grignard reagent (2 equiv) in THF was stirred at −15 °C for 5 min then at room temperature for 30 min. C: After a mixture of the substrate and Et_2AlCl (2 equiv) in THF was stirred at −15 °C for 5 min, the Grignard reagent (2 equiv) was added and the mixture was stirred at room temperature for 30 min. [c] Isolated yield after chromatographic purification.

tricyclic *N,O*-acetals **12**−**14** (see Table 1) with construction of the morphan skeleton.

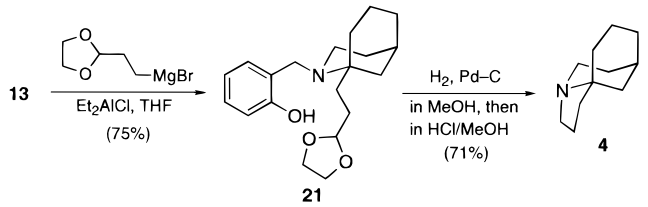
We then explored the possibility of introduction of an alkyl group onto the bridgehead position of the morphan core in the tricyclic *N,O*-acetals **12**−**14** with organometallic reagents. With this aim we first employed **12** and, according to our previous procedure for the formation of "hydrazonium ions" from the hydrazine *N,O*-acetals,[4] we performed the substitution reaction using 2.5 equiv of Et_3Al as a Lewis acid with a nucleophilic alkyl group, resulting in alkylation of the bridgehead position to afford **15a** in 75% yield (Table 1, entry 1). When the allyl Grignard reagent was employed without adding a Lewis acid, only a trace of the 1-allylated product **15b** was observed (entry 2). This result suggested that the ability of Lewis acid to induce the Grignard addition is necessary to allow the initial formation of the iminium ion in agreement with our previous observations.[4b] Thus, **12** was treated with Et_2AlCl (2 equiv), which sufficiently activates the *N,O*-acetal to cleave the C−O bond leading to the iminium ion, and then the Grignard reagents (2 equiv), providing the corresponding 1-alkylated morphans **15a**−**c** in good yields (entries 2−5). This methodology based on Lewis acid induced C−C bond formation was successfully applied to **13** and **14**, giving rise to the 1-alkylated morphans **16** (entries 6−8) and **17** (entries 9−12) in good to excellent isolated yields. The benzylic substitution on the nitrogen in **16a** and **16b** could be readily removed by hydrogenolysis over Pd−C to give the 2-alkylmorphans **2**, wherein R = Et (68% yield) and Pr (70% yield), respectively.

The results of the bridgehead alkylation obtained herein are consistent with an S_N1 mechanism described in Scheme 2. In this reaction Et_2AlCl (or Et_3Al) acts as Lewis acid to weaken the C−O bond in **18**, promoting the formation of the reactive bridgehead iminium ion pair to **19**. Subsequent nucleophilic attack on **19** by the Grignard reagents (or internal delivery[4b] of the ethyl group via **19′** in the case where Et_3Al was used) leads to the 1-alkylmorphan **20**, wherein C−C bond formation proceeds with no stereochemical ambiguity with regard to the newly created stereogenic center at C-1, since attack on only one face is enforced by the rigid bicyclic system.

Scheme 2



Scheme 3



With the required introduction of the alkyl group onto the bridgehead carbon atom of the morphan framework in hand, we proceeded to try to construct the fundamental core ring system of FR901483 (**3**), 5-azatricyclo[6.3.1.$0^{1,5}$]-dodecane (**4**). Thus, **13** was allowed to react with [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide in the presence of Et_2AlCl in THF to give **21** in 75% yield (Scheme 3). Hydrogenation of **21** over Pd−C was initially carried out in MeOH to cleave the 2-hydroxybenzyl group and continued after addition of 3 M HCl, resulting in deacetalization and subsequent in situ iminium ion cyclization and reduction to afford **4** in 71% overall yield.

In conclusion, we have demonstrated that the cyclic *N,O*-acetals could serve as potential precursors for the morphan ring construction and generation of reactive bridgehead iminium ions via Lewis acid treatment, which undergo alkylation with organometallics providing the 1-alkylated morphans. The methodology developed was successfully applied to the synthesis of 5-azatricyclo-[6.3.1.$0^{1,5}$]dodecane.

Supporting Information Available: Experimental procedures and analytical and spectral data for compounds **2** (R = Et and Pr), **4**, **9**−**14**, **15a**−**c**, **16a**−**c**, **17a**−**c**, and **21** (11 pages).

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