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Enantioselective Deprotonation of the 8-Oxabicyclo[3.2.1]octan-3-one: Synthesis of 8-Oxa-norcocaines and 8-Oxa-pseudonorcocaines.

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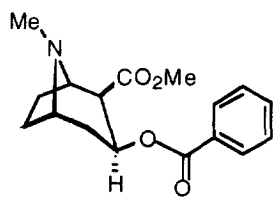
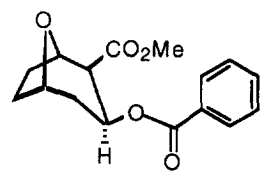
Abstract: The enantioselective deprotonation of the 8-oxabicyclo[3.2.1]octan-3-one with chiral lithium amides **5** and **6**, in the presence of LiCl, gave the chiral lithium enolates which were in turn reacted with methyl cyanoformate. The resulting chiral β-keto esters were reduced with sodium amalgam to afford the 8-oxa-ecgonine- and 8-oxa-pseudoecgonine-like derivatives which allowed facile preparation of the (+)- and (-)-8-oxa-norcocaines and (+)- and (-)-8-oxa-pseudonorcocaines. The new synthesized 8-oxa analogues of cocaine showed good enantiomeric excesses in the range of 84-90%.

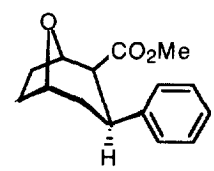
With the aim of obtaining cocaine antagonists or "partial agonists" for possible use in abuse therapy, particular attention has been devoted recently to the discovery of cocaine analogues that show high affinity binding to the cocaine recognition site on the dopamine transporter, but low potency in the inhibition of dopamine uptake.[1,2] The study of cocaine analogues differing sterically or electronically from the parent structure is a logical starting point in the quest for such molecules.[1,3,4] In particular, in terms of exploring new areas of structural alteration to cocaine, we believed that it would be informative to examine the effect of replacing cocaine's bridge nitrogen atom by an oxygen atom.



(-)-cocaine (**1**)



(-)-8-oxa-norcocaine (**2**)



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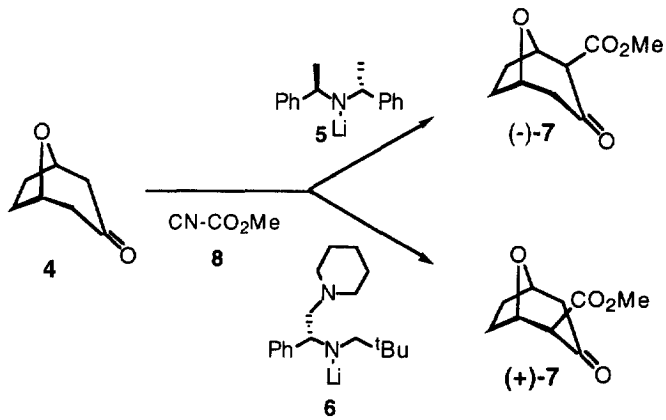
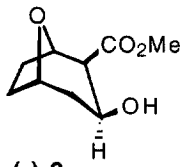
Such molecules would provide relevant information to the question of whether cocaine binds to its recognition site in its protonated or non-protonated form. A search of the literature revealed that oxygen analogues of cocaine had, in fact, been known for some time with the first synthesis of the 8-oxa-norcocaine (**2**) being reported by Brownbridge and Chan[5] in 1979, and a second route being reported in 1990 by Kainz and Eiden.[6] In the latter report, these authors generated all four possible diastereomeric products. However, in spite of this earlier synthetic work, we found no reports concerning the biological activity of any of these products. Additionally, all reported compounds were prepared in racemic form. Recently, an interesting 3-phenyl bearing analog **3** of 8-oxa-norcocaine (a compound related to the so-called WIN series of cocaine) was reported by Meltzer *et al.* as a potent non-nitrogen containing inhibitor of monoamine transporters.[7] In order to avoid potential problems stemming from the study of racemic materials, we have investigated methods aimed at obtaining the 8-oxa-norcocaine **2** and its diastereomers in non-racemic form. In this communication we describe for the first time the enantioselective synthesis of the (+)- and (-)-oxa-norcocaines **2** and the (+)- and (-)-oxa-pseudonorcocaines **11** *via* the enantioselective deprotonation of the known 8-oxabicyclo [3.2.1] octan-3-one **4**.

Homochiral lithium amide (HCLA) bases have been found to serve as important new reagents for asymmetric synthesis, allowing kinetically controlled deprotonations of cyclic ketones to afford good discrimination between enantiotopic α-hydrogens.[8-11] In particular, Simpkins *et al.* have described the asymmetric transformation of the ketone **4** into non-racemic enol silanes by use of HCLA bases.[12] Also, Majewski and Lazny have used such a desymmetrisation process as the starting point in the synthesis of a number of alkaloids and natural cocaine-related structures.[13] They demonstrated that the chiral bases **5** and **6**, developed by Simpkins and Koga,[14] work efficiently in the asymmetric deprotonation of tropinone.[13]

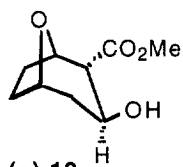


Thus, it seemed to us that HCLA methodology could offer an attractive means for procuring the non-racemic oxa-norcocaines. It appeared evident that ready access to **2** could be achieved by simple enantioselective deprotonation of the ketone **4**. Thus, when the 8-oxabicyclo [3.2.1] octan-3-one **4** was deprotonated by the chiral lithium amide **5** and reacted with methyl cyanoformate, under the same conditions as reported by Majewski,[13] we obtained the non-racemic β-ketoester (-)-**7**. Considering that sodium amalgam reduction of the 2-carbomethoxytropinone is still the easiest route to produce ecgonine methyl ester, the intermediate **7** was reduced with this reagent to produce the two alcohols derivatives (-)-**9** and (+)-**10** having good ee

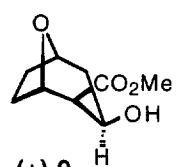
(84 and 88% respectively). The reduction of the β–ketoester **7** was also attempted with sodium borohydride but inseparable mixtures of the four diastereoisomers were obtained and the desired cocaine-like derivative was present only in traces.



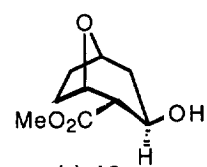
(-)-9



(+)-10

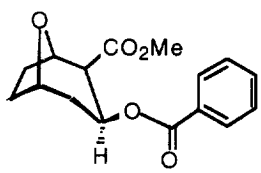


(+)-9

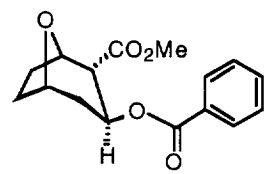


(-)-10

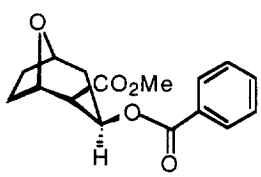
Finally, benzoylation of the β–hydroxy esters (-)-**9** and (+)-**10** was performed with benzoyl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP); the reaction yielded the desired (-)-(8)-oxa-norcocaine **2** and (+)-(8)-oxa-pseudonorcocaine **11** in good yield and reasonable optical purity.



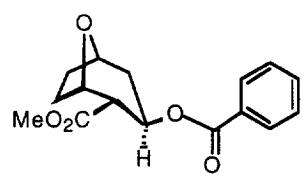
(-)-8-oxa-norcocaine (**2**)



(+)-8-oxa-pseudonorcocaine (**11**)



(+)-8-oxa-norcocaine (**2**)



(-)-8-oxa-pseudonorcocaine (**11**)

The bidentate HCLA base **6** was used instead of *ent*-**5** to gain access to (+)-**7**. Surprisingly, attempts to obtain (+)-**7** using *ent*-**5** was less satisfactory. Finally, reduction of (+)-**7** with sodium amalgam and then benzoylation of the alcohols (+)-**9** and (-)-**10** produced the desired (+)-(8)-oxa-norcocaine **2** and (-)-(8)-oxa-pseudonorcocaine **11** in 83 and 84% ee, respectively. Optical purities were determined by gas chromatography on a commercially available chiral column.[15] In light of the chemical correlations reported by Majewski and Lazny[13] in the conversion of tropinone to cocaine-related products, and the chemical correlations carried out by Simpkins *et al.* using 8-oxabicyclo [3.2.1] octan-3-one as substrate, it is possible to assign the absolute stereochemistry of (-)-oxa-norcocaine to be the same as that of (-)-norcocaine.[16]

In conclusion, an enantioselective synthetic pathway for the construction of 8-oxa-norcocaines has been delineated and has further demonstrated the importance of asymmetric transformations mediated by chiral lithium amide bases. Owing to the easy availability of the starting ketone **4**, as well as the simplicity of the methodology, one may expect its broad application for the construction of a variety of chiral derivatives of

8-oxa-norcocaine. It is noteworthy that the synthetic methodology described above also allowed facile assignment of the absolute configuration of the synthesized oxa-norcocaines. Interestingly, preliminary biological experiments reveal that (-)-**2**, while less active than either cocaine or norcocaine, still retains activity both in the binding and dopamine uptake inhibition studies [binding affinity (Ki) of 4.2 ± 0.03 μM; dopamine uptake (Ki) of 8.5 ± 1.0 μM]. These pharmacological findings support our earlier suggestion that cocaine is likely to bind in its neutral form to the DAT. Full synthetic and biological details of this work will be reported separately.

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15 For the determination of the enantiomeric excesses of our synthesized chiral compounds the solvent delivery system consisted of a Jasco Bip I HPLC pump equipped with a Reodyne Model 7125 injector with a 20 μl sample loop. The eluents were monitored by an UV Detector set at 270 nm and the chromatographic column was a Chiral OD (250x4.6 mmI.D.) Daicel Chemical Industries, LTD. The mobile phase composition was a 2-propanol-hexane solution. (-)-**9**, $[\alpha]_D$ -55.85° (*c* 1, $CHCl_3$), 84 % ee; (+)-**9**, $[\alpha]_D$ +58.9° (*c* 0.5, $CHCl_3$), 90 % ee; (+)-**10**, $[\alpha]_D$ +23.4° (*c* 0.5, $CHCl_3$), 88 % ee; (-)-**10**, $[\alpha]_D$ -22.5° (*c* 0.5, $CHCl_3$), 84 % ee; (-)-**2**, $[\alpha]_D$ -43.9° (*c* 0.5, $CHCl_3$), 85 % ee; (+)-**2**, $[\alpha]_D$ +41.7° (*c* 0.5, $CHCl_3$), 83 % ee; (+)-**11**, $[\alpha]_D$ +60.4° (*c* 0.5, $CHCl_3$), 89 % ee; (-)-**11**, $[\alpha]_D$ -55.6° (*c* 0.5, $CHCl_3$), 83 % ee.

16 Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001. These authors have proposed the preparation of a 6,7-dehydro analog of **7** using the HCLA methodology.