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Oxazatricyclic Noradamantanes: Stereocontrolled Synthesis of Functionalized Scopolines, Related Cage Molecules, and Drug Leads

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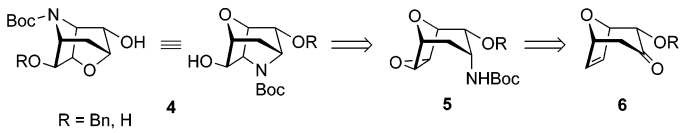
ABSTRACT



Scopolines 4 and the noradamantane scaffold are accessible from 8-oxabicyclo[3.2.1]oct-6-en-3-ones such as 6 by a concise route involving introduction of an axial amino nitrogen at C3, epoxidation, and cyclization. The resulting cage molecules are versatile drug leads.

Tropane alkaloids occur in plants of the family *Solanaceae* and show a diverse pharmacological profile. They are used medicinally, e.g., as anticholinergics, competing with acetylcholine for the muscarinic receptor site of the parasympathetic nervous system.[1] Bicyclic tropane alkaloids have been studied intensively as cocaine receptor antagonists.[2] Scopoline **3** (oscine) isolated from *Datura* spp. (Angels' trumpets) is a naturally occurring tricyclic tropane alkaloid formed from scopolamine **1** (hyoscine), a strong cerebral sedative.[3] The use of these broadly applicable alkaloids dates back at least as far as 3000 BC: Native Americans and ancient Hindus smoked selected alkaloidal plants during ritualistic ceremonies. The problem of defining their utility as a medicinal agent is complicated by the fact that the plant produces a large number of closely related alkaloids, and those present in larger relative quantity are not necessarily those with the more interesting medicinal properties.

Scopoline **3** occurs only in small amounts in nature. Pharmacological studies of scopoline derivatives have indicated analgesic activity,[4] surface anesthetic activity,[5] and antispasmodic, antisecretory, anti-Parkinson, and tranquilizing effects (travel sickness).[6] The biosynthetic route to scopoline **3** implicates epoxy alcohol scopine **2**. Under achiral conditions this *meso*-configured intermediate is desymmetrized to (±)-**3** (Scheme 1).[7]

A useful route to tropane alkaloids is the [4 + 3] cycloaddition of pyrroles to oxyallyls,[8] reported several years ago: oxyallyls are typically generated from α,α'-dibromo ketones with NaI/Cu,[8a] $Fe_2(CO)_9$,[8b] or Et_2Zn.[8c] It occurred to us that scopoline can be regarded as a dihetero analogue

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(1) Derwick, P. M. *Medicinal Natural Products*; Wiley: Chichester, UK, 1998; Chapter 6.
(2) Reviews: (a) Singh, S. *Chem. Rev.* **2000**, *100*, 925. (b) Fodor, G. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1997; Vol. 4, pp 4251−4276.
(3) (a) Heusner, A. *Chem. Ber.* **1954**, *87*, 1063. (b) Fodor, G.; Kovacs, O. *J. Chem. Soc.* **1953**, 2341. (c) Stereochemistry and configuration of scopolamine: Fodor, G. *Tetrahedron* **1957**, *1*, 86.
(4) Waters, J. A.; Creveling, C. R.; Witkop, B. *J. Med. Chem.* **1974**, *17*, 488.
(5) Zeile, K.; Heusner, A. *Chem. Ber.* **1957**, *90*, 2800−2809.
(6) Zaugg, H. E. U.S. Patent 2,927,925, 1960; *Chem. Abstr.* **1960**, *54*, 14293.
(7) Enzymatic resolution of (±)-scopoline: Cramer, N.; Laschat, S.; Baro, A. *Synlett* **2003**, 2178.

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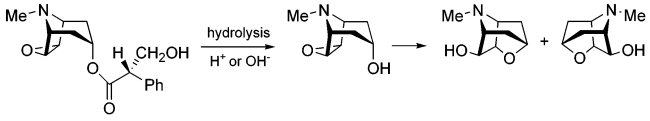
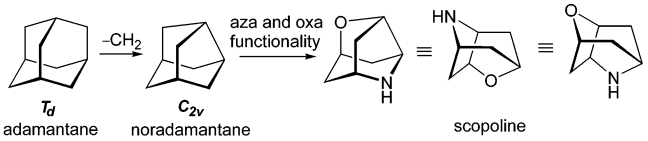
Scheme 1. Biosynthetic Route to Scopoline **3**



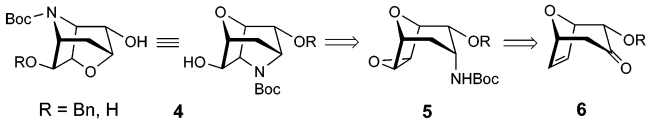
of noradamantane. Removal of any one of the six methylene groups in adamantane generates a zero-bridge between two of the four bridgeheads. Simultaneously the high T_d symmetry (24 symmetry operations) of adamantane is lowered to C_{2v} (4 symmetry operations). Site-selective introduction of oxygen and nitrogen into the noradamantane scaffold provides the asymmetric scopoline framework (arbitrary absolute configuration) (Scheme 2).

Scheme 2. Gedanken Experiment Linking Adamantane and Scopoline



Accordingly, scopoline and many derivatives should be accessible in nonobvious fashion by *delayed introduction* of amino nitrogen, starting from 8-oxabicyclo[3.2.1]oct-6-en-3-ones **6** (Scheme 3).[9] Epoxidation and cyclization involving nitrogen as internal nucleophile were envisioned to yield the oxazatricyclic noradamantane scaffold **4**.[10]

Scheme 3. Retrosynthesis of Functionalized 2-Oxa-6-azatricyclo[3.3.1.0^{3,7}]nonanes **4**[a]



[a] Only one enantiomer shown for clarity.

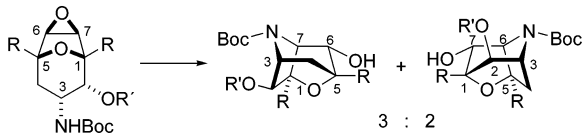
We started from 2α-benzyloxy bicyclics **8a,b** that are available from **7** on a multigram scale[11] and submitted them to reductive amination.[12a] Only the axial amines **9a,b** were obtained. Best results were achieved with $NaBH_3CN$ in the presence of dry NH_4OAc (Table 1, entries 2 and 3). Experiments with $NaBH(OAc)_3$[12b] were not successful.

Table 1. Stereocontrolled Reductive Amination of Oxabicyclic Ketones **7a,b**

entry		R	R′	conditions	product	yield [%]
1	**8a**	H	H	NH_4OAc, $NaBH(OAc)_3$, MeOH, rt, 2−3 d	**9a**	nr
2	**8a**	H	H	NH_4OAc, $NaBH_3CN$, MeOH, rt, 2−3 d	**9a**	55
3	**8b**	Me	H	NH_4OAc, $NaBH_3CN$, MeOH, rt, 2−3 d	**9bα**	90
4	**8b**	Me	PhCH(Me)	$PhCH(Me)NH_2$, $NaBH_3CN$, MeOH, 5N HCl in MeOH, rt, 2−3d	**9bβ**	40

Protection of the basic nitrogen in **9a,b** as *N*-Boc derivatives and epoxidation proceeded smoothly, giving the cyclization precursors **10a,b**. Cyclization to 2-oxa-6-azatricyclo-[3.3.1.0^{3,7}]nonanes **11** and **12** was tried under a variety of conditions. Grignard reagents such as *tert*-butylmagnesium chloride gave the desired oxazatricyclics **11** and **12** in good to high yield (Table 2). The bulky Grignard reagent appears to function first as a base and then as a Lewis acid, activating

Table 2. Cycloisomerization of Tricyclic Amino Epoxides to Functionalized Scopolines[a]



entry		R	R′	conditions	products	yield [%]
1	**10a**	H	Bn	*t*BuMgCl, THF, 0 °C to rt, 2 h	**11a, 12a**	60
2	**10a**	H	Bn	PrMgCl, THF, 0 °C to rt, 4 h	**11a, 12a**	61
3	**10b**	Me	Bn	PrMgCl, THF, 0 °C to rt, 4 h	**11b, 12b**	75
4	**10b**	Me	Bn	PrMgCl, THF, 0 °C to rt, 65 h	**11b, 12b**	68
5	**10b**	Me	Bn	*t*BuMgCl, THF, 0 °C to rt, 2 h	**11b, 12b**	77
6	**10-OH**	Me	H	*t*BuMgCl, THF, 0 °C to rt, 2 h	**11-OH, 12-OH**	70

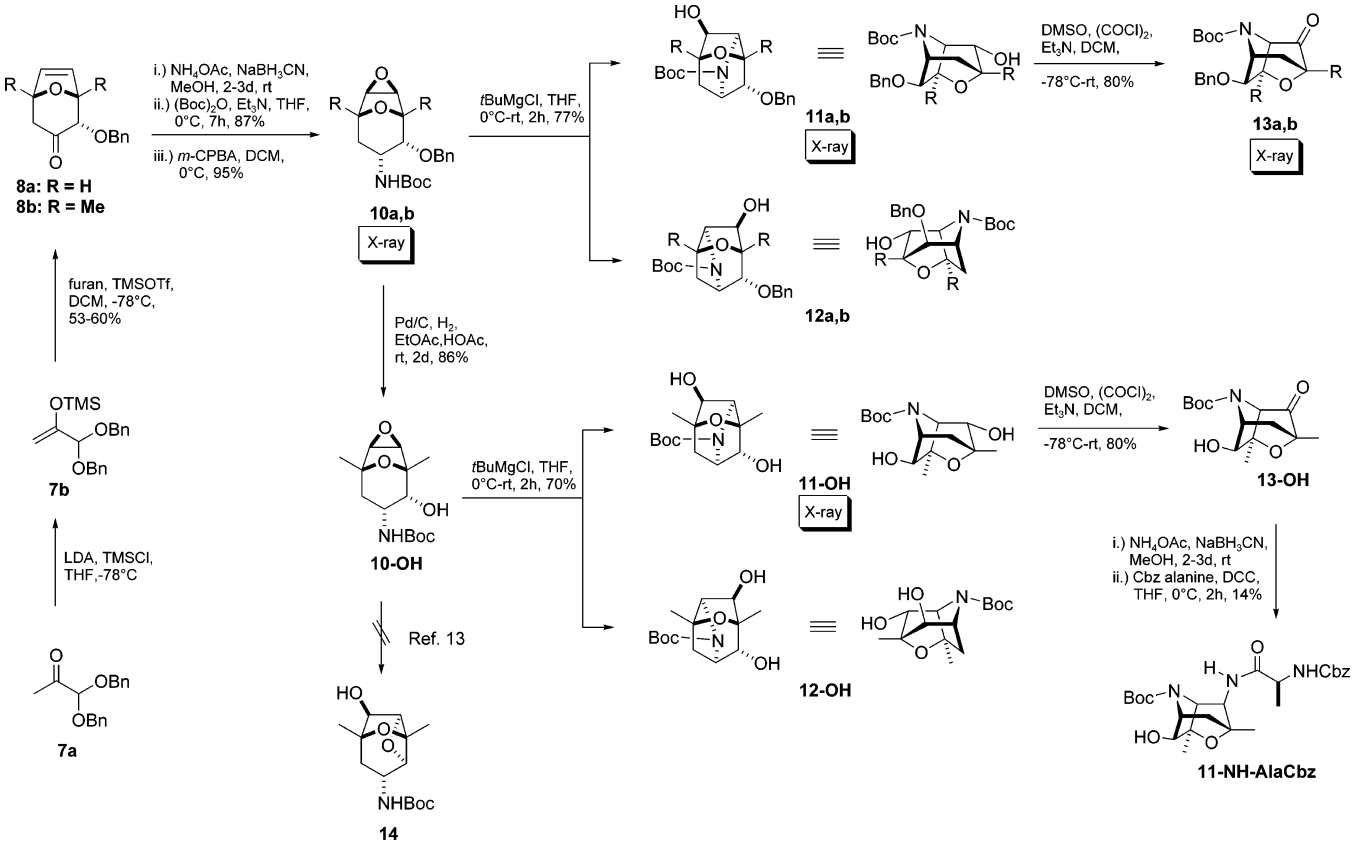
(8) (a) Fierz, G.; Chidgey, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 410. (b) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786. (c) Mann, J.; Barbosa, L.-C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787. See, however: Hodgson, D. M.; Paruch, E. *Tetrahedron* **2004**, *60*, 5185. The classical Robinson tropinone synthesis proceeds with umpolung of reactivity from three-carbon and four-carbon building blocks. See: Robinson, R. *J. Chem. Soc.* **1917**, 762.

(9) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934.

(10) Compare also synthesis of epibatidine: Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. R.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771.

(11) Experimental procedure submitted to *Org. Synth.*, available on e-mail request from the corresponding author.

Scheme 4. Functionalized Scopoline Synthesis Exemplified



the epoxide. The relative orientation of functional groups in the major product **11** and the more "cocaine-like" structure of minor product **12** are noteworthy and generate further interesting stereochemical issues. For example, in **12** the oxygen at C2 is axial with respect to the piperidine and equatorial with respect to the tetrahydropyran segment.

The X-ray crystal structure of **10a** shows that the amino nitrogen is not equidistant from epoxide carbon C6 and C7. Rather the distance N−C7 is shorter (3.06 Å) than N−C6 (3.12 Å) (Figure 1). Internal attack of amino nitrogen results

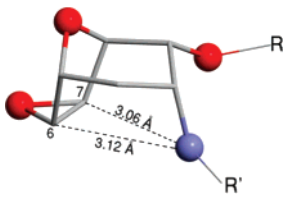


Figure 1. Truncated X-ray structure of **10a**. All hydrogen atoms are omitted.

in oxazatricyclics **11** and **12** in the ratio of 3:2, indicating preferred nucleophilic attack of the more proximate epoxide carbon C7, irrespective of possible obviating factors such as the orientation and precise nature of the nucleophile under the experimental conditions.

Debenzylation of **10b** and treatment of the resulting *N*-Boc-protected epoxy amino alcohol **10-OH** with *tert*-butylmagnesium chloride gave the hydroxylated scopoline skeleton **11-OH** (Scheme 4) rather than dioxatricyclic dictyoxetane skeleton **14**, which is another cage molecule and drug lead.[13] Again a regiopreference (3:2) of ring closure of precursor **10-OH** to form major diol **11-OH** and minor diol **12-OH** was observed (Scheme 4).

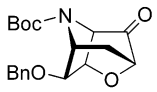
2-Oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonanes **11a,b** were easily oxidized to crystalline ketones **13a,b**. Diol **11-OH** afforded keto alcohol **13-OH** by site-selective Swern oxidation of the more accessible hydroxy group. Reductive amination of keto alcohol **13-OH** and the introduction of *NH*-Cbz-protected alanine gave the weakly antitumor active peptide **11-NH-AlaCbz**.

The oxaza tricycles **10**, **11**, and **13** were tested for biological activity, derivative **13a** being most active toward carcinoma type HMO 2 (gastric carcinoma), HEP G2 (hepatic carcinoma), and MCF 7 (mamma carcinoma) (Table 3). To our knowledge, this is the first time that antitumor activity has been observed for this class of compounds.

(12) (a) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1. (b) Abdel-Magid, A. F.; Garson, K. G.; Harris, B. D.; Maryanoff, C. A., Shaw, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(13) (a) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *1*, 368. (b) Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1998**, *39*, 8259. (c) Proemmel, S.; Hoffmann, H. M. R.; Beil, W. *Tetrahedron* **2002**, *58*, 6199.

Table 3. Antitumor Activity for **13a** (in μg/mL)[14]



13a

	HMO2	HEP G2	MCF 7
GI50	0.17	0.16	0.38
TGI	0.26	0.25	0.42
LC50	0.42	1.8	4.4

In assessing the scope and utility of our protocol for the construction of noradamantanes and related small-molecule NCEs,[15] the following points should be borne in mind: (i) Diversity connecting points for combinatorial studies can be installed at all peripheral carbon atoms of the densely functionalized noradamantane skeleton, including the four bridgehead carbons. These four sites are often the most difficult to functionalize by traditional methodology. (ii) Heteroatom combinations other than O and N are feasible. Mono-hetero noradamantanes are accessible from cyclopentadiene [4 + 3] cycloadducts. (iii) The resolution of racemic cage molecules can be notoriously difficult. Our asymmetric cycloaddition utilizing the enantiopure α-methylbenzyl auxiliary [cf. **6**, R = (*R*)- or (*S*)-CH(Me)Ph][16] instead of the *O*-benzyl group (**6**, R = $PhCH_2$) allows stereocontrol of up to four stereocenters and then seven in all. Hence our work also constitutes a formal total synthesis of enantiopure oxazatricyclic noradamantanes, scopolines, and related cage molecules, which do not occur in the natural series. (iv) Tuning of lipophilicity/hydrophilicity along the Lipinski rules[17] of drug design is feasible.

Finally, the growing potential of [4 + 3] cycloadducts and the wide applicability of 8-oxabicyclo[3.2.1]oct-6-en-3-ones[9] are underscored.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, the Volkswagen Foundation, and the Fonds der Chemischen Industrie for support.

Supporting Information Available: Preparation of (±)-2-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one **8a** and also **8b** (see ref 11), spectroscopic data of nine tricyclics and bicyclics, and supplementary crystallographic data for four tricycles (see ref 18). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) GI50 = concentration causing 50% growth inhibition; TGI = concentration causing 100% growth inhibition; LC50 = concentration causing 50% reduction of the cells present.

(15) New Chemical Entity; see: Rouhi, A. M. *Chem. Eng. News* **2003**, Oct 13, 77, *93*, 104.

(16) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1266. Pierau, S.; Hoffmann, H. M. R. *Synlett* **1999**, 213. Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 684. Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883.

(17) Lipinski, C. A. *Drug Discovery Today* **2003**, *8*, 12.

(18) CCDC 240296 (**10a**), CCDC 240294 (**11b**), CCDC 240297 (**11-OH**), and CCDC 240295 (**13a**) can be obtained from the Cambridge Crystallographic Data Centre, deposit@ccdc.cam.ac.uk.