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Enantioselective Access to Isoquinuclidines by Tropenone Desymmetrization and Homoallylic Radical Rearrangement: Synthesis of (+)-Ibogamine

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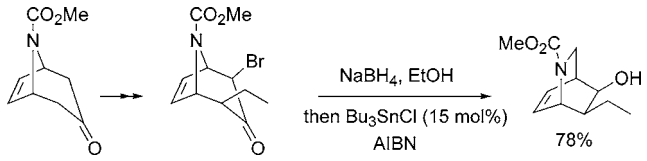
ABSTRACT



Chiral lithium amide-induced desymmetrization of a tropenone and subsequent Bu_3SnH-catalyzed nitrogen-directed homoallylic radical rearrangement constitute key steps in a new strategy to dehydroisoquinuclidines. The strategy was applied in a synthesis of (+)-ibogamine.

Isoquinuclidines (2-azabicyclo[2.2.2]octanes) constitute the structural centerpiece in many bioactive natural products such as the *iboga* alkaloids catharanthine and ibogamine **1** (Figure 1),[1] as well as in nonindole-containing alkaloids such as the cannivonines and dioscorine **2**.[2] Moreover, in medicinal chemistry, the isoquinuclidine ring system is frequently employed as a rigid azabicyclic scaffold.[3] Isoquinuclidines are often prepared by [4 + 2] cycloadditions of unstable dihydropyridines;[4] however, only a few methods for the asymmetric synthesis of functionalized isoquinuclidines have been reported.[5]

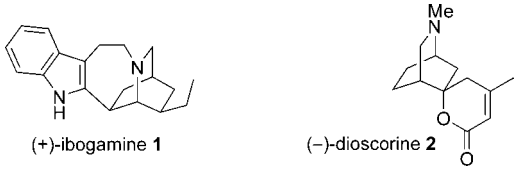


Figure 1. Ibogamine **1** and dioscorine **2**.

In the present paper, we present a new and enantioselective access to 5,6-dehydroisoquinuclidines and an application of this methodology to the synthesis of (+)-ibogamine **1**. The approach builds on our recently developed nitrogen-directed homoallylic rearrangements of 7-azabicyclo[2.2.1]heptenyl systems.[6] Extension of this methodology to 8-azabicyclo-

(1) (a) Sundberg, R. J.; Smith, S. Q. *The Alkaloids* **2002**, *59*, 281−386. (b) For a recent synthesis of ibogamine **1**, see: White, J. D.; Choi, Y. *Helv. Chem. Acta* **2002**, *85*, 4306−4327.

(2) Page, C. B.; Pinder, A. R. *J. Chem. Soc.* **1964**, 4811−4816.

(3) Iriepa, I.; Villasante, F. J.; Gálvez, E.; Labeaga, L.; Innerarity, A.; Orjales, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 189−192.

(4) For a discussion in the context of the *iboga* isoquinuclidine ring system, see: Maia, A. A.; Freitas-Gil, R. P.; Gil, L. F.; Marazano, C. *Lett. Org. Chem.* **2004**, *1*, 168−170.

(5) For some examples, see: (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332−2342. (b) dos Santos, D. C.; de Freitas Gil, R. P.; Gil, L.; Marazano, C. *Tetrahedron Lett.* **2001**, *42*, 6109−6111. (c) Höck, S.; Koch, F.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **2004**, *15*, 1801−1808.

(6) (a) Hodgson, D. M.; Bebbington, M. W. P.; Willis, P. *Org. Biomol. Chem.* **2003**, *1*, 3787−3798. (b) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815−817.

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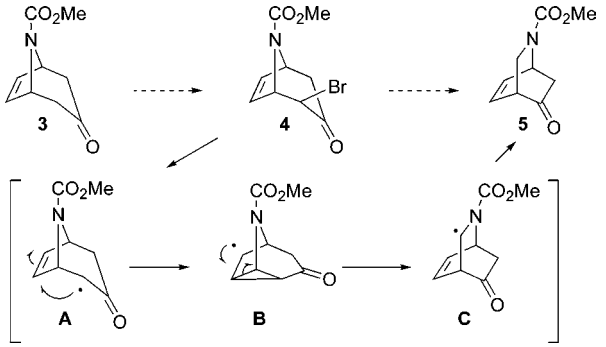
[3.2.1]octenes would, if successful, provide a novel entry to dehydroisoquinuclidines (Scheme 1).[7] Enantioselective de-

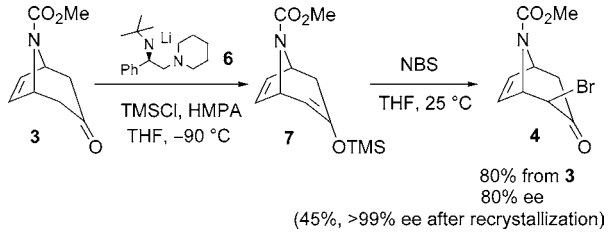
Scheme 1



symmetrization of tropenone **3**[8] was envisaged to give radical precursor **4**, which was anticipated to lead (after homoallylic rearrangement, **A**→**C**) to dehydroisoquinuclidinone **5** (Scheme 1).

To examine the above chemistry, tropenone **3** was prepared by [4 + 3] cycloaddition from commercially available *N*-(carbomethoxy)pyrrole and 1,1,3,3-tetrabromoacetone,[9] as developed by Mann and de Almeida Barbosa in 55% yield.[10] With tropenone **3** in hand, we screened a number of chiral bases to effect enantioselective enolization. From these studies, chiral lithium amide (*R*)-**6**[11] was found to give the best results. Thus, reaction of tropenone **3** with lithium amide (*R*)-**6** in the presence of HMPA (2 equiv) and TMSCl (3 equiv) at −90 °C in THF gave crude silyl enol ether **7** (Scheme 2). Without further purification, silyl enol

Scheme 2

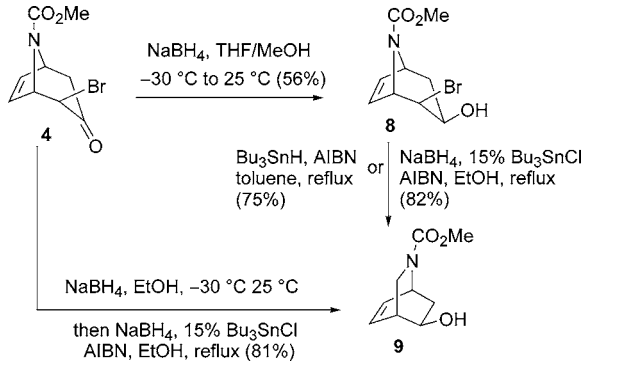


ether **7** was treated with NBS (1.1 equiv) in THF at 0 °C for 10 min to give α-bromoketone **4** in 80% ee (by chiral GC analysis) and in 80% yield from tropenone **3**. α-Bromoketone **4** was recrystallized twice from Et_2O−petroleum ether (bp 30−40 °C) to provide material of >99% ee (45% yield from tropenone **3**). The absolute configuration of α-bromoketone **4** was determined by X-ray crystallographic analysis[12] and is as shown in Scheme 2. The sense of asymmetric induction with lithium amide (*R*)-**6** is in accord with previous results.[8,13]

α-Bromoketone **4** was then subjected to standard radical rearrangement conditions as previously reported by us.[6] Thus, slow addition (over 1 or 2 h) of 1.5 equiv of Bu_3SnH or tris(trimethylsilyl)silane (TTMSS) and AIBN to a boiling solution of α-bromoketone **4** in toluene gave in each case only directly reduced tropenone **3** in ∼70% yield. None of the desired dehydroisoquinuclidinone **5** was isolated. These observations could be due to the fact that, and in contrast with our earlier work, the first generated radical species in the present case **A** (Scheme 1) is capto-stabilized by the α-keto group. On the basis of this analysis, removal or modification of the carbonyl functionality was deemed necessary.

Deoxygenation of the carbonyl group to a methylene group or protection of the keto functionality was not successful (possibly due to the presence of the bromine substituent). However, reduction of the keto group in α-bromoketone **4** to a hydroxyl group could be achieved to give bromohydrin **8** (Scheme 3). The best conditions found for the reduction

Scheme 3



were using $NaBH_4$ in THF−MeOH (1:1) at temperatures from −30 to 25 °C,[14] which gave bromohydrin **8** as a single stereoisomer[15] in 56% yield (its high solubility in water might account for the modest yield). Pleasingly, when bromohydrin **8** was reacted with Bu_3SnH, a clean homoallylic radical rearrangement occurred to give enantiopure dehydroisoquinuclidinol **9** as the sole product in 75% yield. Interestingly, this process could also be carried out in 82% yield without a slow addition protocol and with significantly reduced

(7) For a related homoallylic radical rearrangement of a tropane derivative leading to a 6-azabicyclo[3.2.1]octane, see: Rigby, J. H.; Pigge, F. C. *Tetrahedron Lett.* **1996**, *37*, 2201−2204.

(8) For a related desymmetrization of a carbamate-protected (saturated) tropinone, see: Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1307−1313.

(9) Kim, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **2000**, 2195−2201.

(10) Mann, J.; de Almeida Barbosa, L.-C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787−790.

(11) Curthbertson, E.; O'Brien, P.; Towers, T. D. *Synthesis* **2001**, 693−695.

(12) CDCC 265105 available at http://www.ccdc.cam.ac.uk.

(13) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1315−1321.

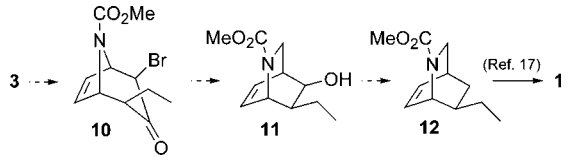
(14) Careful control of the temperature is necessary to avoid competitive removal of the bromine substituent, followed by further reduction. Very slow warming up of the cooling bath must be performed with a critical stage around −15 °C where most of the reduction occurs.

(15) CDCC 265106 available at http://www.ccdc.cam.ac.uk.

quantities of a stannane precursor by using $NaBH_4$ (1.5 equiv), AIBN, and Bu_3SnCl (15 mol %) in EtOH at reflux.[16] This last result led us to investigate a one-pot ketone reduction−homoallylic radical rearrangement sequence, which gave dehydroisoquinuclidinol **9** directly from α-bromoketone **4** in 81% yield.

We next sought to apply the homoallylic rearrangement methodology to a more complex structure and selected ibogamine **1** as a target to demonstrate the utility and flexibility of our approach. We initially focused on accessing dehydroisoquinuclidine **12** (Scheme 4), since it was a

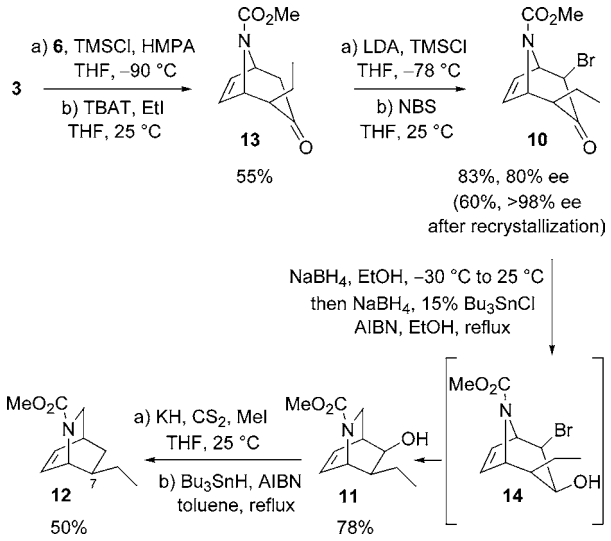
Scheme 4



previously reported intermediate by Krow and co-workers en route to ibogamine **1**.[17] Dehydroisoquinuclidine **12** was anticipated to be available from deoxygenation of dehydroisoquinuclidinol **11**, itself obtained via reduction−homoallylic rearrangement of α,α′-disubstituted ketone **10** (Scheme 4). Ketone **10** in turn might be accessed via enantioselective α-ethylation and subsequent α′-bromination of tropenone **3**.

Precedent for direct enolization−alkylation of ketones is usually restricted to methylation, allylation, and benzylation, with primary linear alkyl electrophiles being rather unreactive. Indeed, attempted alkylation of the lithium enolate of tropenone **3** with EtI as an electrophile was unsuccessful. More encouraging was benzyltrimethylammonium fluoride (BTAF)-induced ethylation[18] of silyl enol ether **7**, which gave the alkylated ketone **13** (Scheme 5) in up to 40% yield as a

Scheme 5

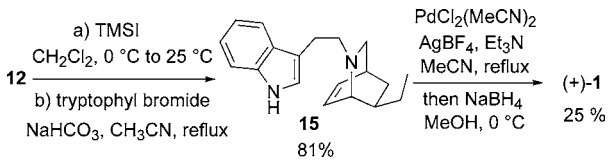


single stereoisomer. However, dry BTAF is difficult to handle (being very hygroscopic), and the yields of **13** were somewhat capricious. The use of the nonhygroscopic and commercially available fluoride source tetrabutylammonium triphenyldifluorosilicate (TBAT) delivered a more satisfactory solution,[19] providing alkylated ketone **13** in a reproducible 55% yield (86% based on recovered tropenone **3**).

NBS-induced bromination of the kinetic silyl enol ether of ketone **13** gave α,α′-disubstituted ketone **10** (83%, 80% ee); material of >98% ee (60% from ketone **13**) was obtained following a single recrystallization from Et_2O−petroleum ether. Bromohydrin **14** could be obtained (78%)[20] from α,α′-disubstituted ketone **10** and $NaBH_4$ by following the protocol used earlier to prepare bromohydrin **8**. X-ray crystallographic analysis of bromohydrin **14**[21] indicated an all-*exo* configuration for the three stereocenters introduced from tropenone **3**. Pleasingly, the one-pot ketone reduction−homoallylic radical rearrangement sequence developed earlier cleanly converted α,α′-disubstituted ketone **10** into dehydroisoquinuclidinol **11** (78%).[22] Formation of the xanthate of dehydroisoquinuclidinol **11**, followed by radical deoxygenation, gave dehydroisoquinuclidine **12** in 52% overall yield. We were surprised to find that the NMR data of dehydroisoquinuclidine **12** did not match those previously ascribed to *rac*-**12** by Krow and co-workers[17] but rather matched the data assigned by them to the 7-ethyl epimer. As the configuration of the ethyl group in our sequence is supported by crystallographic analyses, this indicates that the wrongly assigned epimer (7-*epi*-**12**) was in fact progressed toward ibogamine **1** by Krow and co-workers.[23]

In seeking a more concise route to ibogamine **1** than that investigated by Krow and co-workers,[17,24] we focused on converting dehydroisoquinuclidine **12** into Trost's ibogamine precursor **15** (Scheme 6).[25]

Scheme 6



Deprotection of dehydroisoquinuclidine **12** and N-alkylation[26] with tryptophyl bromide afforded Trost's ibogamine

(16) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555.
(17) Krow, G. R.; Shaw, D. A.; Lynch, B.; Lester, W.; Szczepanski, S. W.; Raghavachari, R.; Derome, A. E. *J. Org. Chem.* **1988**, *53*, 2258−2262.
(18) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025−1030.
(19) (a) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1986**, *51*, 6901−6905. (b) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129−1131.
(20) See Supporting Information.
(21) CDCC 265107 available at http://www.cdcc.cam.ac.uk.
(22) CDCC 265108 available at http://www.ccdc.cam.ac.uk.
(23) In light of our results, Prof. Krow reassessed the NMR experiments originally used to assign **12** and 7-*epi*-**12** in ref 17 and agrees that the C-7 stereochemical assignments should be reversed.
(24) Synthesis of **1** would require ~10 further steps from **12**. See also: Imanishi, T.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1985**, *33*, 4202−4211.

precursor **15** in 81% yield. Finally, we repeated the Pd(II)−Ag(I) mixed-metal-mediated cyclization developed by Trost and co-workers,[27] albeit with less success than originally reported, to provide after reductive workup (+)-ibogamine **1**[28] in 25% yield (40−45% yield was reported for *rac*-**1**).[25,29] Spectral data were in full accord with those obtained in a recent synthesis of (−)-ibogamine **1**.[1b,30]

In summary, we have developed an efficient route to enantioenriched dehydroisoquinuclidines via enantioselective enolization of an achiral tropenone, followed by a stannane-catalyzed homoallylic radical rearrangement. The asymmetric synthesis of (+)-ibogamine **1** demonstrates the potential of this new strategy in the context of natural product synthesis.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc*. **1978**, *100*, 3930−3931.

(26) Kunng, F.-A.; Gu, J.-M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262−4266.

(27) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7−13.

(28) $\alpha]^{23}_{D}$ +42.2 (*c* 0.29, EtOH), lit. (Dickel, D. F.; Holden, C. L.; Maxfield, R. C.; Paszek, L. E.; Taylor, W. I. *J. Am. Chem. Soc*. **1958**, *80*, 123−125) $[\alpha]^{23}_{D}$ −36.4 ($CHCl_3$), lit.[1b] $[\alpha]^{23}_{D}$ −45.8 (*c* 0.2, EtOH).

(29) Ethyl epimer of **1** has also been previously prepared using Trost's cyclization procedure, in 20% yield, see: Tomisawa, H.; Hongo, H.; Kato, H.; Sato, K.; Fujita, R. *Heterocycles* **1981**, *16*, 1947−1950.

(30) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373−2376.