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A NOVEL APPROACH TO IBOGA ALKALOIDS: TOTAL SYNTHESIS OF (±)-IBOGAMINE AND (±)-*epi*-IBOGAMINE

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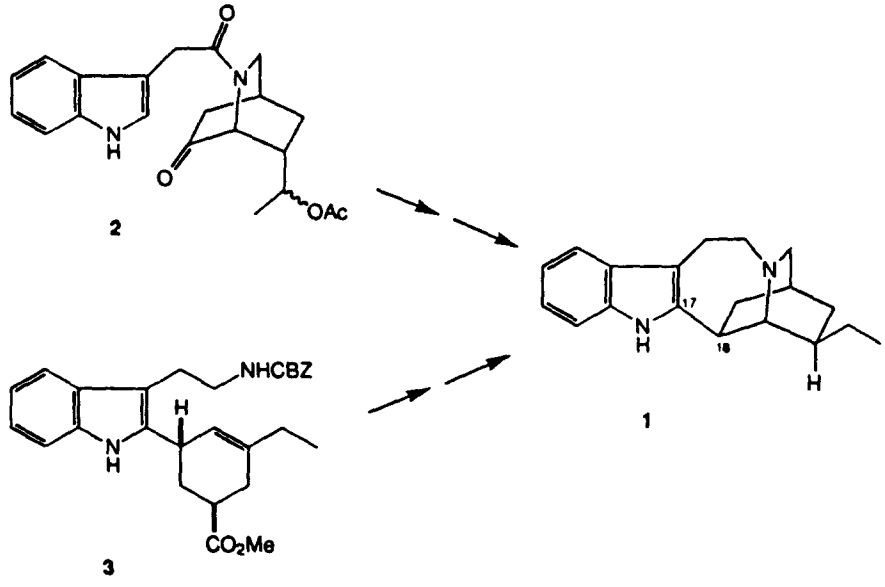
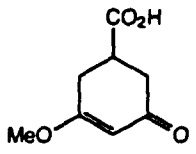
Abstract: A novel approach to the total synthesis of (±)-ibogamine and (±)-*epi*-ibogamine, featuring electrophilic substitution at C(2) of N'-CBZ-tryptamine by an allylic acetate, is described. Copyright © 1996 Elsevier Science Ltd

Since Büchi's total synthesis of (±)-ibogamine (**1**) in 1965,[1] the vast majority of the syntheses of **1** reported have adopted the strategy of generating N-β-(indolylethyl)isoquinuclidines followed by cyclization leading to the formation of the hydroazepine ring (cf **2** → **1**).[2] We detail below a synthesis of ibogamine which features prior formation of the C(17), C(18) carbon-carbon bond of **1** *via* direct introduction of a carbocyclic ring at C(2) of N'-CBZ-tryptamine, followed by seven-membered hydroazepine ring formation and subsequent elaboration of the isoquinuclidine (cf **3**→**1**).



Implementation of our strategy begins with the known vinylogous ester **4**,[3] which was readily available from 3,5-dimethoxybenzoic acid. Exposure of **4** to excess ethylmagnesium bromide followed by acid hydrolysis and esterification(diazomethane) afforded a 73% yield of **5**. Luche reduction[4] gave rise to a near quantitative yield of **6** as a 4:1 mixture of cis and trans allylic alcohols which was purified and used directly in the next reaction. Prolonged exposure (48 h) of **6**, 0.2 M in 5.0 M $LiClO_4$-Et_2O, to 2.0 equiv of



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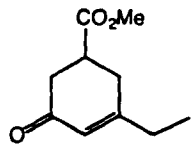

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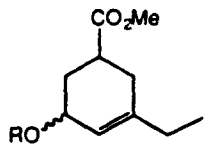
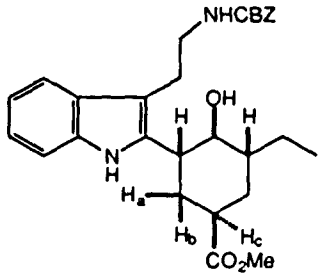


6 R = H
7 R = Ac

N'-carbobenzyloxytryptamine[5] and 0.05 equiv of camphorsulfonic acid[6] gave rise to a 60% yield of crystalline **3**, mp 123-124 °C. The formation of **3** could also be carried out employing allylic acetate **7** in the presence of lithium cobalt-bis-dicarbollide, $Li[Co(B_9C_2H_{11})_2]$,[7a] as a catalyst, thus avoiding the use of a concentrated solution of lithium perchlorate in diethyl ether.[7b] Thus, addition of 10 mol% lithium cobalt-bis-dicarbollide to a 0.1 M solution of allylic acetate **7** in refluxing 1,2-dichloroethane containing 2.0 equiv of N'-carbobenzyloxytryptamine gave rise after 8 h to a 60% yield of **3**.

With all the necessary atoms for elaboration of the ibogamine skeleton assembled, efforts were directed to hydroazepine ring formation. Toward this end, olefin **3** was exposed (0 °C, 3 h) to 3.0 equiv of diborane in tetrahydrofuran. Standard workup with base/hydrogen peroxide gave a 68% yield of a single alcohol **8**, mp 152-154 °C. ^1H NMR analysis of **8** at 500 MHz revealed that both the carbinol proton and the proton adjacent

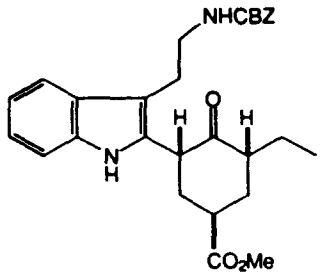


8

to the indole exhibit large couplings, indicating that both protons experience *trans*-diaxial interactions with vicinal protons. This observation is consistent with hydroboration from the least hindered face of the double bond. In addition, extensive decoupling studies revealed that the coupling constant between the axial proton H_b and H_c is ca. 5 Hz which is consistent with structure **8** wherein the hydroxyl and carbmethoxy group are *syn* to each other.

With the stereochemistry of the ethyl group set properly relative to the indole moiety, attention was directed to construction of the seven membered hydroazepine ring by intramolecular reductive amination of the corresponding ketone (**9**). Attempts to oxidize **8** in the presence of the unprotected indole with standard oxidants gave rise to complex mixtures with only trace quantities of **9** present. Attempts to use the Saigo-Mukaiyama protocol,[8] which had proved invaluable in conjunction with a total synthesis of yuehchukene,[6b] wherein a primaary alcohol was oxidized in the presence of an unprotected indole, failed to give rise to **9**. Use of the Dess-Martin periodinane also failed giving rise to extensive decomposition. Fortunately use of the

hypervalent iodine species **10**[9,10] proved successful. Exposure (4 h) of **8** to 2.0 equiv of **10** in methylene chloride at ambient temperature afforded a 75% yield of ketone **9**, mp 150-151 °C.



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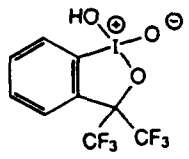

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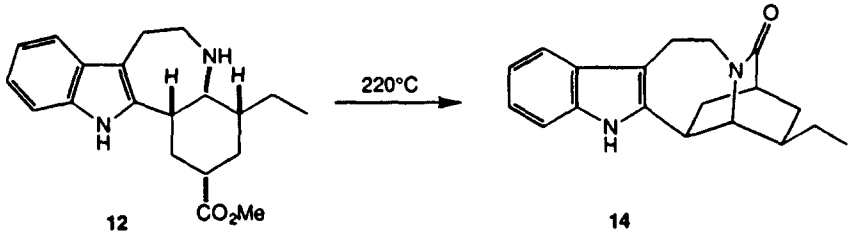
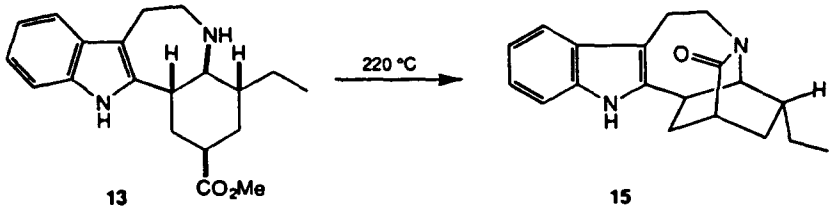
Removal of the nitrogen protecting group was best affected under a modification of the conditions described by Jackson and Johnstone for catalytic transfer hydrogenation.[11] Ketone **9** was exposed to 10% palladium on carbon in 1:1 tetrahydrofuran-ethanol in a sealed vessel at 80 °C using cyclohexene as the hydrogen source. After 40 min, the mixture was filtered through celite under nitrogen with dry tetrahydrofuran and treated at ambient temperature for 2 h with excess sodium cyanoborohydride and trifluoroacetic acid.[12] Workup provided **12**, mp 158-159 °C, and **13**, mp 122-123 °C, in 75% overall yield in a ration of 1:2.4. The structures assigned to **12** and **13** were based on extensive ^{1}H NMR decoupling experiments.

Pyrolysis of the minor diastereomer **12** at 220 °C under argon for 2 h gave rise to a 77% yield of a single crystalline lactam **14**, whose ^{1}H NMR spectrum was identical to that reported in the literature for 19-oxoibogamine.[2i] Reduction of **14** with lithium aluminum hydride (THF, 70 °C, 6 h) afforded (±)-ibogamine,

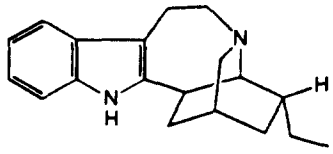


12 **14**

mp 128-131 °C (lit[1] mp 129-132 °C) in 75% yield. The diastereomeric tetrahydroazepine **13** upon intramolecular lactamization (220 °C) provided (78%) **15** which upon reduction ($LiAlH_4$, THF, 70 °C, 6 h) gave rise to (±)-*epi*-ibogamine (**16**), mp 199-201 °C (lit[1] mp 193-197 °C).



13 **15**



16

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References

1. Büchi, G.; Coffen, D.L.; Kocsis, K.; Sonnet, P.E.; Ziegler, F.E. *J. Am. Chem. Soc.* **1965**, *87*, 2073. Büchi, G.; Coffen, D.L.; Kocsis, K.; Sonnet, P.E.; Ziegler, F.E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.

2. For previous syntheses of ibogamine, see: a) Sallay, S.I. *J. Am. Chem. Soc.* **1967**, *89*, 6762. b) Nagata, W.; Hirai, S.; Okumura, T.; Kawata, K. *J. Am. Chem. Soc.* **1968**, *90*, 1650. c) Ikezaki, M.; Wakamatsu, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1969**, 88. d) Rosenmund, P.; Haase, W.H.; Bauer, J.; Frische, R. *Chem. Ber.* **1975**, *108*, 1871. e) Trost, B.M.; Godleski, S.A.; Genet, J.P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. f) Atta-ur-Rahman; Beisler, J.A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063. g) Imanishi, T.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1985**, *33*, 4202. h) Huffman, J.W.; Shanmugasundaram, G.; Sawdaye, R.; Raveendranath, P.C.; Desai, R.D. *J. Org. Chem.* **1985**, *50*, 1460. i) Kuehne, M.E.; Reider, P.J. *J. Org. Chem.* **1985**, *50*, 1464.

3. Kuehne, M.E.; Lambert, B.F. *J. Am. Chem. Soc.* **1959**, *81*, 4278.

4. Gemal, A.L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

5. Freter, K.; Weissbach, H.; Redfield, B.; Udenfriend, S.; Witkop, B. *J. Am. Chem. Soc.* ***1958***, 80, 983.

6. For the reactions of allylic alcohols with indoles see: a) Pearson, W.H.; Schkeryantz, J.M. *J. Org. Chem.* **1992**, *57*, 2986. b) Henry, K.J., Jr.; Grieco, P.A. *J. Chem. Soc. Chem. Commun.* **1993**, 510.

7. (a) For the use of $Li[Co(B_9C_2H_{11})_2]$ as a catalyst for the conjugate addition of silyl ketene acetals to α,β-unsaturated carbonyl compounds, see: DuBay, W.J.; Grieco, P.A.; Todd, L.J. *J. Org. Chem.* **1994**, *59*, 6898. (b) Grieco, P.A.; DuBay, W.J.; Todd, L.J. *Tetrahedron Lett.* in press.

8. Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1977**, *50*, 2773.

9. Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

10. For use of the hypervalent iodine species **10** in organic synthesis, see: VanderRoest, J.M.; Grieco, P.A. *J. Am. Chem. Soc.* **1993**, *115*, 5841. Grieco, P.A.; Collins, J.L.; Moher, E.D.; Fleck, T.J.; Gross, R.S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

11. Jackson, A.E.; Johnstone, R.A.W. *Synthesis* **1976**, 685.

12. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* **1974**, 635.

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