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The Norrish Type I Photo-cleavage of (+)-2β-Ethyl-9-azabicyclo[3.3.1]nonan-3-one: A Short, Enantioselective Formal Synthesis of (-)-Indolizidine 223AB

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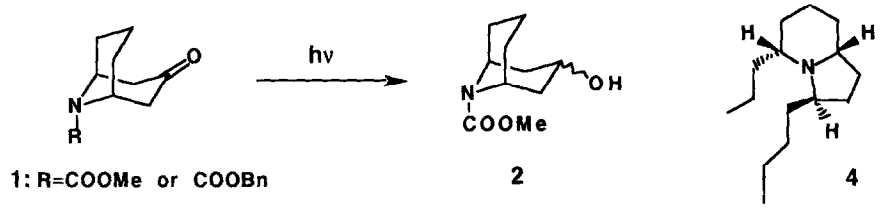
Abstract: The enantioselective alkylation of the "fork head ketone" (**1**) followed by the Norrish Type I photo-cleavage provided the short enantioselective synthesis of (-)-indolizidine 223AB (**4**).

Synthetic applications of the Norrish Type I reaction of cyclic ketones[1] rely on the regioselectivity of the α-cleavage. Thus the group of Roberts has reported the synthesis of various prostaglandins based on the Norrish Type I reaction of cyclobutanones.[2] In our continuing studies on the use of bridged bicyclic compounds as the synthon for the natural product synthesis,[3] we previously reported the photo-reactivity of 9-azabicyclo[3.3.1]nonan-3-one (**1**, R=COOMe), where characteristic photo-reduction occurred to give the corresponding bicyclic alcohol, 9-azabicyclo[3.3.1]nonan-3-ol (**2**), in moderate yield.[4]

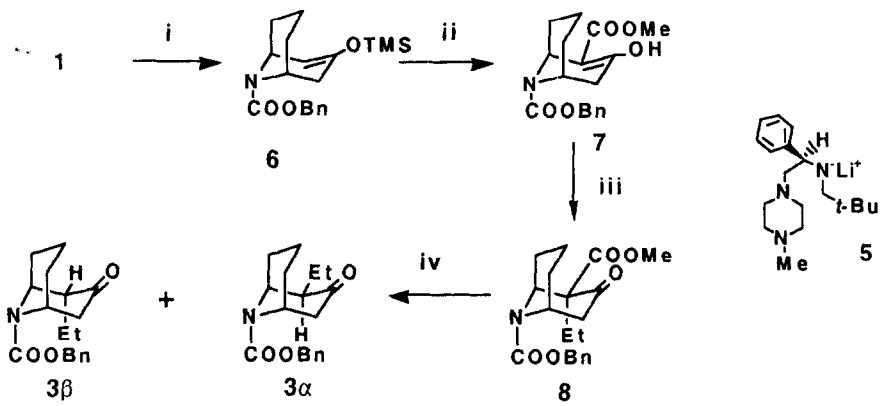


1: R=COOMe or COOBn **2** **4**

In this paper we describe the photo-irradiation of the system bearing the ring appendage ethyl at the position α to the 'fork head' carbonyl, 9-benzyloxycarbonyl-2-ethyl-9-azabicyclo[3.3.1]nonan-3-one (**3**). Effective α-cleavage of the system provided an efficient enantioselective route to (-)-indolizidine 223AB (**4**), one of the neurotoxin alkaloids isolated in minute quantity from skin extracts of neotropical poison-dart frogs

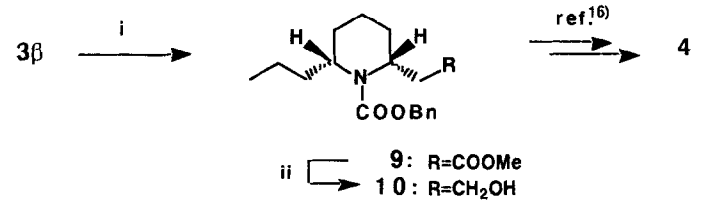
(family Dendrobatidae).[5,6] Because of its unusual biological characteristics, **4** has been the target of many synthetic efforts.[7]

Koga and co-workers have reported the effective enantioselective deprotonation of cyclic carbonyl compounds.[8] We applied their procedure to the dissymmetrization of **1** in order to obtain a homochiral reactant (+)-**3** for the enantioselective synthesis of (-)-**4**. Thus the ketone (**1**, R=$COOCH_2C_6H_5$) was treated with the homochiral lithium amide (**5**) and excess trimethylsilyl chloride in tetrahydrofuran (THF) at -100 °C to give the corresponding trimethylsilyl enolate[9] (**6**, $[\alpha]_D^{26}$ -19.0) in ≥94% e.e. and in 96% c.y. The enol ether (**6**) was treated with methyl lithium at -60 °C, and the subsequent Claisen condensation of the resulting enolate with methyl cyanoformate[10] gave methyl (1*S*, 5*R*)-(+)-9-(benzyloxycarbonyl)-3-hydroxy-9-azabicyclo[3.3.1]non-2-ene-2-carboxylate (**7**) in 77% yield. The β-keto ester (**7**) was then subjected to alkylation with ethyl iodide in the presence of sodium hydride in THF to afford *exo*-ethyl bicyclic β-keto ester, methyl (1*S*, 2*R*, 5*R*)-(+)-9-(benzyloxycarbonyl)-2-ethyl-3-oxo-9-azabicyclo[3.3.1]nonane-2-carboxylate (**8**), in 91% yield. The ketonic cleavage of **8** by action of a 3% potassium hydroxide solution in aqueous dimethylsulfoxide afforded two epimeric 2-ethyl ketones, (1*S*, 2*S*, 5*R*)-(+)-2β- and (1*S*, 2*R*, 5*R*)-(+)-2α-ethyl-9-azabicyclo[3.3.1]nonan-3-one (3β and 3α[11]) in a ratio of 5 : 4. The e.e. of 3β was determined to be 94%[12] on the basis of the HPLC measurements.



i) 5, TMSCl, HMPA, -100°C, THF; ii) NCCOOMe, MeLi, HMPA, -60°C, THF
iii) EtI, NaH, THF, MeOH, reflux; iV) KOH, DMSO, H_2O, 120°C

Photo-irradiation[13] of 3α in methanol through a Pyrex filter caused dealkylation[14] to give the parent ketone **1** along with a small amount of the α-cleaved product, methyl (2*R*, 6*R*)-(-)-1-benzyloxycarbonyl-6-propylpiperidine-2-acetate (**9**).[15] In contrast, irradiation of the epimer 3β in methanol for 5 h gave the desired α-cleaved piperidine (**9**) in 66% yield. The selective reduction of **9** with diisobutylaluminum hydride at -10°C afforded (2*R*, 6*R*)-(+)-1-benzyloxycarbonyl-2-(2-hydroxyethyl)-6-propylpiperidine (**10**) in 75% yield.



i) hv, MeOH; ii) DIBAL-H, -10°C

The effective transformation of **10** to the title compound has already been established in our previous work.[16] Further investigation to transform **1** to other indolizidine alkaloids is now in progress.

References and Notes

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2. Newton, R.F. in "Photochemistry in Organic Synthesis", Coyle, J.D. ed. The Royal Society of Chemistry, 1986, Special Publication No. 57, Chapt. 3 and references cited therein.
3. Syntheses of some naturally occurring products by employing the bridged bicyclic compounds as the starting material have been reported, see for example: a) Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.*, **1990**, 1319. b) Momose, T.; Okumura, K.; Tsujimori, H.; Inokawa, K.; Tanabe, G.; Muraoka, O.; Eugster, C.H. *Heterocycles*, **1993**, *36*, 7. c) Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull.*, **1990**, *38*, 2072.
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7. For (-)-**4**: a) Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Asymmetry*, **1993**, *4*, 1429. b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.*, **1992**, *57*, 5178. c) Taber, D.F.; Deker, P.B.; Silverberg, L.J. *ibid.*, **1992**, *57*, 5990. d) Roger, J.; Husson, H.-P. *Tetrahedron Lett.*, **1985**, *26*, 1515. For (±)-**4**: e) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.*, **1989**, *54*, 4088. f) *Idem*, *J. Am. Chem. Soc.*, **1985**, *107*, 5534. g) Broka, C.A.; Eng, K.K. *J. Org. Chem.*, **1986**, *51*, 5043. For the stereoisomers of **4**: h) Nakagawa, Y.; Stevens, R.V. *J. Org. Chem.*, **1988**, *53*, 1871. i) Hart, D.J.; Tsai, Y.-M. *ibid.*, **1982**, *47*, 4403. j) Macdonald, T.L. *ibid.*, **1980**, *45*, 193. k) Stevens, R.V. *J. Chem. Soc., Chem. Commun.*, **1982**, 103.
8. Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.*, **1986**, *108*, 543.
9. Spectral properties and absolute configuration of **6** were referred to those of the methyl carbamate analog previously synthesized, see ref. 3a.
10. Izawa, H.; Shirai, R.; Kawasaki, H.; Kim, H.-D.; Koga, K. *Tetrahedron Lett.*, **1989**, *30*, 7221.
11. For the synthesis of racemic **3**, see ref. 3b.
12. The value was determined by HPLC on the chiral column AS (Daicel Chemical Industries, Ltd.) using a mixture of *n*-hexane, ethanol, and 2-propanol (10 : 1: 1, v/v) as an eluent.

13. The photo-irradiation was carried out in an immersion apparatus fitted with an Ishii UV-HT 400W high pressure mercury lamp under an argon atmosphere.
14. The elimination of the equatorial side chain at the α-position on cyclohexanone ring *via* Norrish type II reaction was reported, see: Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Schore, N. *Acc. Chem. Res.*, **1972**, *5*, 92.
15. Satisfactory physical and spectral data were obtained for all new compounds: for example, for **9**: a colorless oil, bp 166-168 °C (0.008 mmHg). $[\alpha]_D^{24}$ +32.9 (c 0.76, $CHCl_3$). IR ($CHCl_3$): 2950, 1731, 1675, 1413, 1320, 1271, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J*=7.2), 1.16-1.72 (10H, m), 2.55 (1H, dd, *J*=15.0, 4.5), 2.63 (1H, dd, *J*=15.0, 10.5), 3.64 (3H, s), 4.18 (1H, br), 4.71 (1H, br), 5.21 (1H, d, *J*=13.0), 5.16 (1H, d, *J*=13.0), 7.28-7.38 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.0 (t), 14.0 (q), 20.5 (t), 27.1 (t), 28.0 (t), 36.8 (t), 38.9 (t), 47.4 (d), 50.5 (d), 51.6 (q), 67.0 (t), 127.7 (d), 127.8 (d), 128.4 (d), 136.9 (s), 155.7 (s), 171.8 (s). MS *m/z* (%): 333 (M^+, 4), 290 (35), 246 (67), 216 (8), 198 (12), 172 (5), 91 (100), 65 (8). HRMS *m/z*: 333.1924 ($C_{19}H_{27}O_4N$ requires 333.1940).
16. Conversion of **10** to **4** *via* the side chain homologation and cyclization has been achieved, see: Momose, T.; Toyooka, N.; Tojima, M.; Seki, S.; Hirai, Y. 16th Symposium on Progress in Organic Reactions and Syntheses, Tokyo, November, **1990**, Symposium Papers, p. 185.

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