Construction of the tricyclo[5.3.1.0^{1,5}]undecane system by a tandem pinacol rearrangement–ene strategy: a formal synthesis of (±)-perhydrohistrionicotoxin

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An advanced synthetic intermediate 4 for perhydrohistrionicotoxin 5 has been synthesized utilizing a novel tandem pinacol rearrangement–ene reaction as a key step.

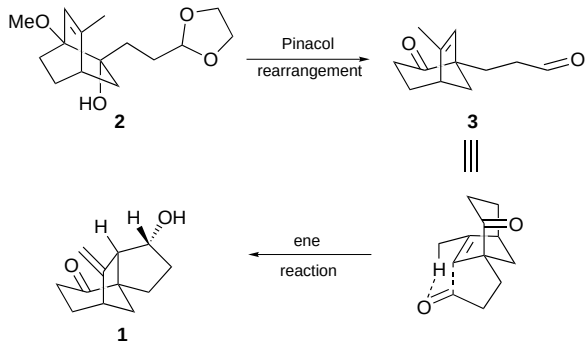
Construction of the tricyclo[5.3.1.0^{1,5}]undecane skeleton, which constitutes the carbon framework of natural products such as cedranes, has been a challenge to synthetic organic chemists and has led to the development of diverse and inspiring strategies.[1] We envisaged that highly functionalized tricyclo[5.3.1.0^{1,5}]undecane system **1** might be accessible by a novel tandem pinacol rearrangement–ene reaction on a Diels–Alder derived bicyclo[2.2.2]octene **2** *via* the intermediacy of bicyclo-[3.2.1]octene derivative **3** (Scheme 1).[2]

Reported herein is a stereoselective synthesis of an advanced intermediate **4**[3] for the synthesis of perhydrohistrionicotoxin **5**,[4] a hydrogenation product of a potent neurotoxin isolated from the Columbian frog *Dendrobates histrionicus*, which demonstrates the potential of our tandem pinacol rearrangement–ene protocol.

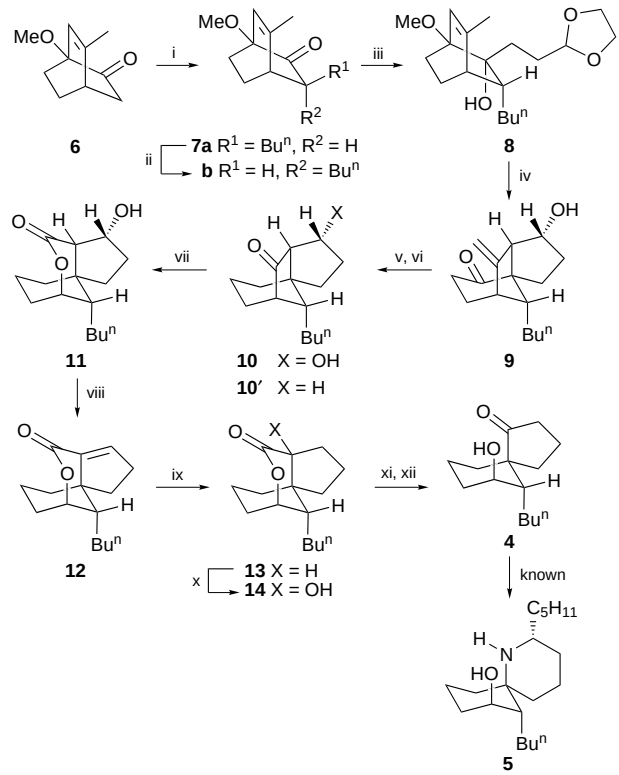
Alkylation of readily available ketone **6**[2a] by successive treatment with LDA and *n*-butyl iodide in THF containing HMPA produced a 75% yield of *exo* product **7a** (Scheme 2). Epimerization of *exo* isomer **7a** with methanolic NaOH produced a chromatographically separable 73 : 27 equilibrium mixture of *exo* and *endo* isomers **7a** and **7b** in a quantitative yield. Treatment of bicyclic ketone **7b**, secured in a large quantity by recycling of **7a**, with appropriate β-bromo ketal derived Grignard reagent under Barbier conditions[5] gave *endo* alcohol **8** in 92% yield stereospecifically. As we had planned, compound **8** underwent an efficient, novel, tandem pinacol rearrangement–ene reaction upon exposure to TsOH in refluxing acetone to afford tricyclic intermediate **9** and its epimeric alcohol in an 89 : 11 ratio (82% total yield).†

Next, we turned to the conversion of the key tricyclic intermediate **9** to our target compound **4** for a formal synthesis of perhydrohistrionicotoxin **5**. Removal of the keto function from **9** by Wolff–Kishner reduction,‡ followed by ozonolysis of the resulting alkene, produced hydroxy ketone **10** in 51% overall yield for the two steps. Regiospecific Baeyer–Villiger oxidation[6] of ketone **10** with MCPBA and subsequent elimination of the resulting β-hydroxy ester **11** gave α,β-unsaturated δ-lactone **12** (76% overall yield over two steps). Our originally projected synthetic plan for processing the key intermediate **4** by an ammonolysis–Hoffmann rearrangement protocol on **12** was thwarted by difficulties encountered in opening of the lactone. To circumvent these problems, catalytic hydrogenation of the alkene functionality in **12** and subsequent α-hydroxylation of the resulting lactone **13** *via* the method of Davis[7] yielded α-hydroxy lactone **14**. Finally, reductive opening of lactone **14** with $LiAlH_4$ to the corresponding diol, followed by oxidative cleavage with $NaIO_4$, delivered the desired keto alcohol **4** in 66% yield for the four steps from **12**.† ^{1}H and ^{13}C NMR spectral data of compound **4** were in good agreement with those of authentic samples kindly provided by Professors Ibuka and Smith.§

In summary, a formal synthesis of (±)-perhydrohistrionicotoxin **5** has been accomplished utilizing a novel tandem pinacol rearrangement–ene strategy and a regiospecific Baeyer–Villiger



Scheme 1



Scheme 2 *Reagents and conditions*: i, $LN(SiMe_3)_2$, Bu^nI, HMPA, THF, −78 to −20 °C, 3 h, 75%; ii, NaOH, MeOH, room temp., 3.5 h (**7a** : **7b** = 73 : 27), 100%; iii, Mg, $Br(CH_2)_2Br$, 2-(2-bromoethyl)- 1,3-dioxolane, THF, room temp., 1.5 h, 92%; iv, TsOH, acetone, reflux, 11 h, (α : β = 89 : 11), 82%; v, NH_2NH_2, $HOCH_2C(=CH_2)CH_2OH$, KOH, $HO(CH_2)_2OH$, 110 to 190 °C, 8 h; vi, O_3, EtOAc, −78 °C, 4 h, then Ph_3P, EtOAc, room temp., overnight, 51%; vii, MCPBA, $NaHCO_3$, CH_2Cl_2, room temp., 1.5 h, 83%; viii, TsCl, DMAP, Et_3N CH_2Cl_2, reflux, 3.5 h, 92%; ix, H_2, Pd–C, EtOH, room temp., 1.5 h, 97%; x, $KN(SiMe_3)_2$, *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C, 1.5 h; xi, LAH, THF, room temp., 2.5 h, 71% (2 steps); xii, $NaIO_4$, acetone–H_2O (1 : 1), 1 h, 96%

reaction as key steps. Efforts are being made to apply this tandem pinacol–ene strategy to syntheses of other natural products.

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Footnotes and References

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† All new compounds exhibited satisfactory spectroscopic data. The ratio of isomers was determined by capillary GLC analysis and/or analysis of 500 MHz ^{1}H NMR spectra. *Selected data* for **4**: δ_C ($CDCl_3$, 100 MHz) 14.0, 19.0, 20.2, 23.3, 29.1, 30.8, 31.9, 32.7, 35.0, 38.3, 47.7, 54.7, 73.3, 223.4.

‡ Addition of 2-methylenepropane-1,3-diol suppresses reduction of the double bond under these reaction conditions.

§ We thank Professors T. Ibuka (Kyoto University) and A. B. Smith, III (University of Pennsylvania) for copies of spectra of compound **4**.

1 Y. Chen and W. Lin, *Tetrahedron Lett.*, 1992, **33**, 1749 and references cited therein.

2 Pinacol rearrangement of a Diels–Alder derived bicyclo[2.2.2]octene **2** has previously been exploited in the synthesis of various natural products: (*a*) S. A. Monti, S. Chen, Y. Yang, S. Yuan and O. P. Bourgeois, *J. Org. Chem.*, 1978, **43**, 4062; (*b*) S. A. Monti and T. R. Dean, *J. Org. Chem.*, 1982, **47**, 2679 and references cited therein.

3 T. Ibuka, Y. Mitsui, K. Hayashi, H. Minakata and Y. Inubushi, *Tetrahedron Lett.*, 1981, **22**, 4425; E. R. Koft and A. B. Smith, III, *J. Org. Chem.*, 1984, **49**, 832.

4 E. J. Corey, J. F. Arnett and G. N. Widiger, *J. Am. Chem. Soc.*, 1975, **97**, 430 and references cited therein.

5 A. Greiner, *Tetrahedron Lett.*, 1989, **30**, 3547.

6 Baeyer–Villiger reaction of the deoxy ketone **10′**, prepared from **10** by elimination and catalytic hydrogenation, produced the desired lactone **13** and its regioisomeric lactone in a 5 : 1 ratio: T. Ho, in *Polarity Control for Synthesis*, Wiley, New York, 1991, p. 353.

7 F. A. Davis, L. C. Vishwaskarma, J. M. Billmers and J. Finn, *J. Org. Chem.*, 1984, **49**, 3241.

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