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# The use of the aza-Diels–Alder reaction in the synthesis of pinidine and other piperidine alkaloids

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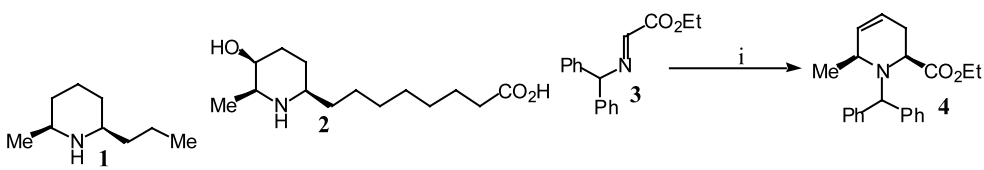
**Abstract**—The imine $Ph_2CHN{=}CHCO_2Et$, generated from benzhydrylamine and ethyl glyoxylate, provides a Diels–Alder adduct with 1,3-pentadiene from which a range of *cis*-2,6-disubstituted piperidines can be accessed; the benzhydryl group confers high diastereocontrol for derivatising the six-membered ring, allowing access to 2,5,6-trisubstituted piperidines, and to 2,6-disubstituted piperidines such as pinidine. 

The piperidine ring is widespread in nature, and these alkaloids possess potent biological properties.[1] Of particular interest to us are pinidine (**1**),[2] and carpamic acid (**2**).[3] In the previous paper, we described aza-Diels–Alder reactions with benzhydryl imine $Ph_2CHN{=}CHCO_2Et$ **3**, which is a stable white solid dienophile that reacts with acyclic dienes to generate piperidines in yields of ca. 70%, with complete control of regio- and diastereochemistry.[4] In this letter, we focus on the use of the penta-1,3-diene adduct,[5] isolated as a single regio- and diastereoisomer (even using an *E*/*Z* mixture of diene), as shown in Scheme 1.

An unexpected feature of these cycloadducts was their conformations. Structural analysis by NMR spectroscopy revealed that *cis*-2,6-substituents in analogues of **4** occupied diaxial (or pseudodiaxial) positions.[6] This led to high diastereocontrol for subsequent transformations, as indicated in Scheme 2, for which hydroboration/oxidation of **4** gave **5**[7] as the sole diastereoisomer. The X-ray crystal structure of the TBDMS protected derivative **7**[8] revealed an all-axial chair conformation of the *C*-substituents, due to the bulky *N*-benzhydryl blocking the 2,6-equatorial positions (Fig. 1). Molecular modelling studies[10] were consistent with the NMR and X-ray observations. As indicated in Figs. 2 and 3, whilst an *N*-benzyl auxiliary can accommodate two flanking equatorial substituents, the bulkier *N*-benzhydryl auxiliary cannot, forcing adjacent substituents into axial positions. This is particularly apparent when the conformation of the global minimum is compared with representative local minima, from which it is apparent that the one phenyl ring can rotate away from steric clashes with adjacent 2,6-diequatorial substituents (*N*-benzyl, Fig. 2), whereas an additional phenyl ring is unable to avoid such a steric interaction (*N*-benzhydryl, Fig. 3). This has dramatic stereochemical consequences on subsequent transformations, which can be exploited to good effect. Thus, whilst the hydroboration/oxidation sequence used to convert **4**→**5** provided the Me/OH *anti* isomer due to the pseudoaxial methyl group, oxidation followed by 'hydride' reduction generated the Me/OH-*syn* isomer of the carpamic acid series, with complete stereocontrol, again conferred by the methyl group due to the influence of the *N*-benzhydryl auxil-




**Scheme 1.** *Reagents and conditions*: (i) penta-1,3-diene (2 equiv.), TFA (1 equiv.), TFE, –40°C (62%).

*Keywords*: alkaloids; Diels–Alder reaction; piperidines.

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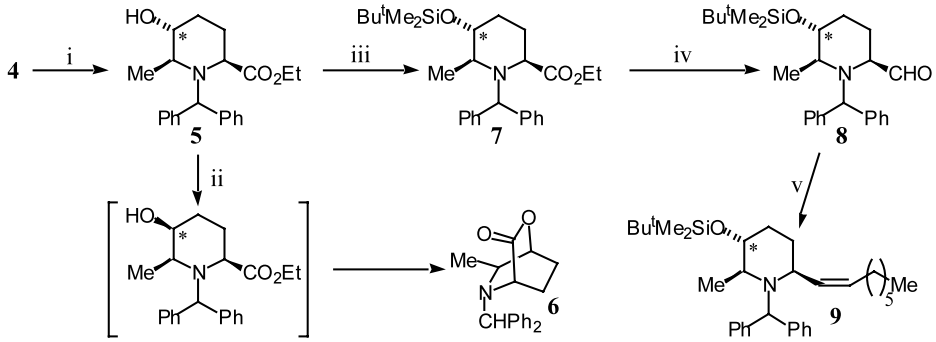


**Scheme 2.** *Reagents and conditions*: (i) $BH_3$·THF, then $H_2O_2$, $HO^-$ (33%); (ii) TPAP, NMO, $CH_2Cl_2$, then L-Selectride (65%); (iii) TBDMS·OTf, DMF (89%); (iv) $LiAlH_4$, $Et_2O$, then Swern oxidation (64%); (v) $n$-$C_7H_{15}PPh_3^+$·$Br^-$, KHMDS, PhMe/THF (74%).

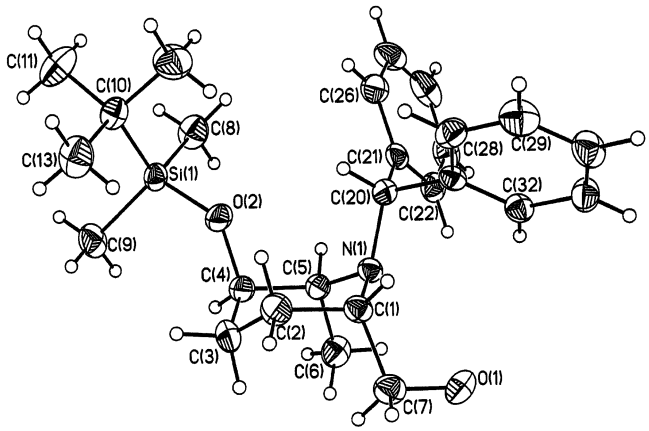


**Figure 1.** X-Ray crystal structure of **7**.[8]

iary; the resulting hydroxyester underwent spontaneous cyclization to the lactone **6**, whose structure was confirmed by NOE studies. Access to the carpamic acid skeleton was demonstrated by the model sequence of reactions shown in Scheme 2. Starting from the protected hydroxyester **7**, reduction with $LiAlH_4$, followed by Swern oxidation, gave the aldehyde **8**; condensation of this with the heptyl triphenylphosphonium ylid gave exclusively the $Z$-alkene **9**, containing the full C/N skeleton of protected carpamic acid, and with control of all three chiral centres.

We have also applied the new aza-Diels–Alder reaction to the synthesis of members of the pinidine family,[2] as summarised in Scheme 3. Thus, the cycloadduct **4** could be reduced to **10** in a single step, which could be converted into the protected aldehyde **11** in high overall

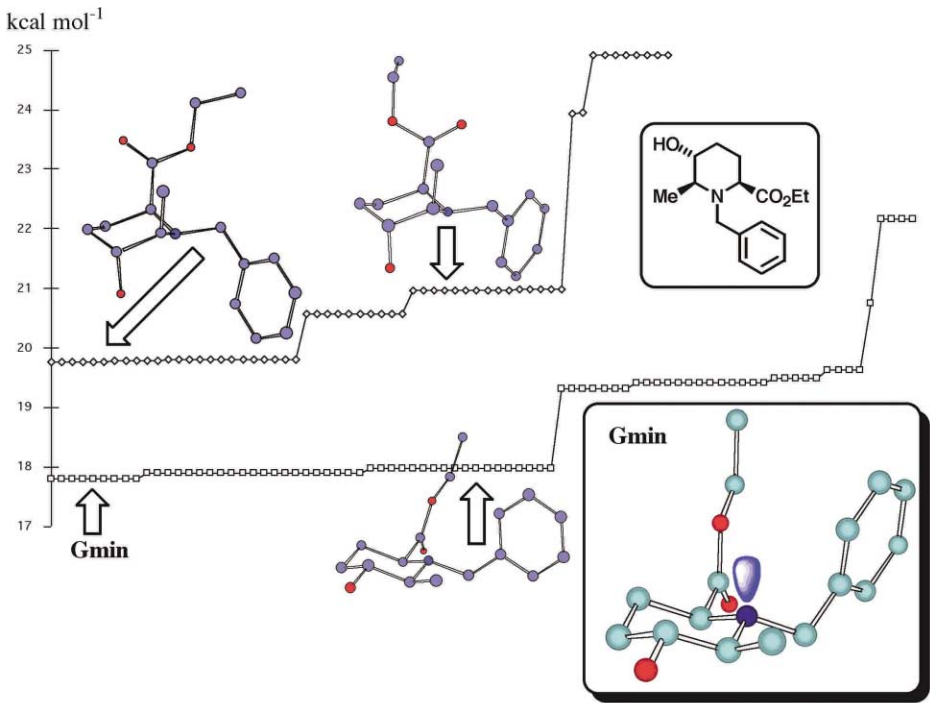


**Figure 2.** Molecular modelling[10] of the $N$-benzyl analogue of **5**. Each point represents a minimised structure from the conformational search. Examples of local minima structures are shown, as well as the global minimum (**Gmin**).

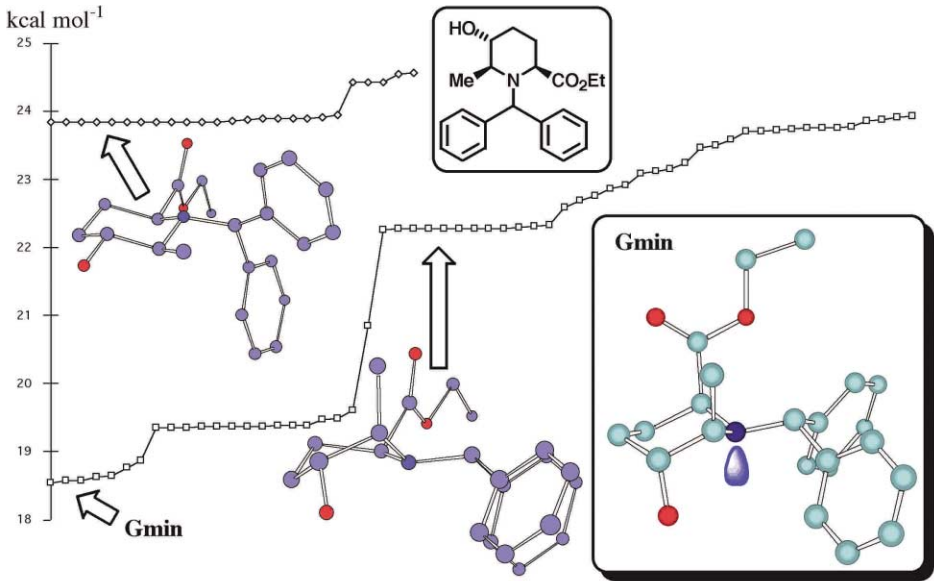
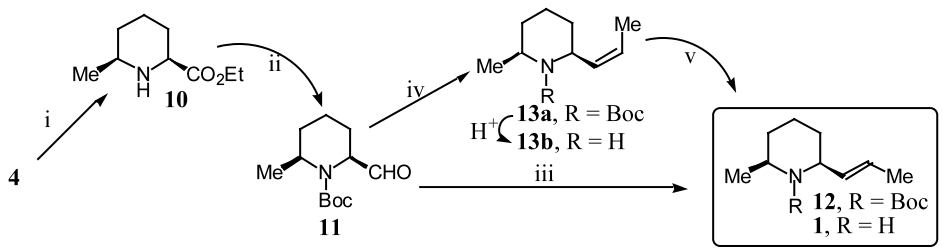



**Figure 3.** Molecular modelling of the *N*-benzhydryl derivative **5** (see Fig. 2 for details).




**Scheme 3.** *Reagents and conditions*: (i) $H_2$, Pd–C, EtOH (70%); (ii) (a) $(Boc)_2O$, $NEt_3$, $H_2O$/dioxan, then (b) $LiBH_4$, $Et_2O$, rt, then (c) TPAP, NMO, $CH_2Cl_2$ (61% overall); (iii) 2-(ethylsulfonyl)benzothiazole, KHMDS, THF, −78°C (34%, *E*/*Z* 6:1); (iv) $Ph_3PEt{\cdot}Br$, KHMDS, THF, rt (91%, all *Z*); (v) UV, $I_2$, 1,2-epoxypropane, hexane, rt (*E*:*Z* 1:1 after 6 h).

yield. The *E*-alkene **12** could be prepared with good stereoselectivity (but poor yield) using modified Julia coupling conditions;[12] alternatively, the *Z*-isomer **13a** could be formed in high yield using Wittig chemistry, and isomerised to the *E*-isomer. Acidic removal of the Boc protection generates *Z*- or *E*-pinidine.

The imine **3** therefore not only provides a reliable and efficient aza-dienophile, but the cycloadduct **4** (from its Diels–Alder reaction with penta-1,3-diene) allows rapid access to alkaloids of the pinidine and carpamic acid families, with the *N*-benzhydryl auxiliary conferring excellent diastereocontrol. We thank Dr. A. S. F. Boyd and Dr. R. Ferguson for NMR and mass spectra, and Quintiles (Scotland) for financial support.

## References

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4. Bailey, P. D.; Smith, P. D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron Lett*. **2002**, *43*, 1067; adduct **4** should allow access to numerous 6-Me-2-substituted piperidines.
5. *1-Benzhydryl-4,5-didehydro-2-ethoxycarbonyl-6-methylpiperidine* **4**: Pale yellow oil; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.96 (3H, d, $J=6.1$ Hz, C6-Me), 1.36 (3H, t, $J=7.1$ Hz), 2.27 (1H, m, C3-$CH_2$), 2.42 (1H, m, C3-$CH_2$), 3.52 (1H, m, C6-CH); 3.66 (1H, dd, $J=6.1$ Hz, 1.6 Hz, C2-CH), 4.13 (2H, q, $J=7.1$ Hz), 5.33 (1H, s, $CHPh_2$), 5.57 (1H, m, C5-CH), 5.82 (1H, m, C4-CH), 7.11–7.31 (6H, m), 7.47–7.56 (4H, m); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 14.19 ($CH_3$), 16.38 ($CH_3$), 24.97 ($CH_2$), 49.73 (CH), 52.44 (CH), 60.23 ($CH_2$), 70.76 (CH), 122.41 (CH alkene), 126.93 (CH alkene), 127.89 (CH), 128.20 (CH), 128.45 (CH), 128.50 (CH), 129.99 (CH), 130.46 (CH), 132.35 (CH), 142.90 (C), 143.47 (C), 175.04 (C=O); IR $\nu$ (thin film, $cm^{-1}$): 3060.6, 3027.7, 2980.2, 2932.5, 1728.7, 1452.4; MS *m*/*z* (EI): 334.8 (0.09%, $M^+$), 320.8 (0.25%, M–$CH_3^+$), 261.9 (14.66% M–$CO_2Et^+$), 166.8 (81.12%, $CHPh_2^+$), 121.0 (100%), 107.1 (100%), 48.9 (21.34%); HRMS calcd for $C_{22}H_{25}NO_2$: 335.1885; found: 335.1891.
6. Although poly-axial conformations of cyclohexanes are rare, *N*-alkyl piperidines can show axial or equatorial preference for 2/6-substituents. See: Bonin, M.; Romero,

J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.

7. *Ethyl 1-benzhydryl-5-hydroxy-6-methylpipecolate* ***5***: White solid, mp 95–96°C; $^1$H NMR (200 MHz, $C_6D_6$): $\delta$ 0.74 (3H, d, $J=7.8$ Hz, C6-Me), 0.87 (3H, t, $J=7.1$ Hz), 1.55 (1H, m, 1 of C3-$CH_2$), 1.78–2.01 (3H, m, 1 of C3-$CH_2$, C4-$CH_2$), 2.43 (1H, s, broad, OH), 3.14 (1H, dq, $J=7.1$ Hz, 2.1 Hz, C6-CH), 3.36 (1H, s, broad, C5-CH), 3.53 (1H, t, $J=3.4$ Hz, C2-CH), 3.77 (2H, dq, $J=7.2$ Hz, 2.56 Hz), 5.72 (1H, s, $CHPh_2$), 6.85–7.08 (6H, m), 7.35–7.47 (4H, m); $^{13}$C NMR (50 MHz, $C_6D_6$): $\delta$ 12.71 ($CH_3$), 13.79 ($CH_3$), 20.62 ($CH_2$), 23.58 ($CH_2$), 53.77 (CH), 54.82 (CH), 59.70 ($CH_2$), 69.17 (CH), 70.25 (CH), 127.57 (CH), 127.69 (CH), 127.93 (CH), 128.14 (CH), 128.18 (CH), 128.51 (CH), 128.66 (CH), 143.16 (C), 143.28 (C), 174.50 (C=O); IR $\nu$ (Nujol, cm$^{-1}$): 3521.1, 3420.8, 1735.6, 1197.3; MS $m/z$ (EI): 354.2 (2.56%, $MH^+$), 280.2 (22.84%, M–$CO_2Et$), 167.1 (100%, $Ph_2CH$). Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.71; H, 7.74; N, 3.90%.
8. *X-Ray data for* ***7***: A single crystal of **7** was covered in Nujol and mounted with vacuum grease on a glass fibre and transferred to a Bruker AXS P4 diffractometer,[9a] and data were measured at 160 K using an Oxford Cryosystems cryostream. Crystal data for **7**: $C_{26}H_{39}NO_2Si$, $M_W=425.67$, monoclinic, space group $P2_1lc$, $a=17.589(4)$, $b=92380(10)$, $c=16.121(4)$ Å, $\beta=108.04(2)°$, $V=2490.7(9)$ Å$^3$, $Z=4$, $D_{calcd}=1.135$ mg m$^{-3}$, $\mu=0.115$ mm$^{-1}$, $T=160(2)$ K. Crystal 0.14×0.68×0.44 mm$^3$, independent reflections 4337 [$R$(int) = 0.0363], $R_1=0.0515$, $wR_2=0.1036$ for [$I>2\sigma(I)$]. Solution and refinement for **7** was performed using the SHELXTL suite of programs.[9b]
9. (a) XSCANS, *Data Collection and Reduction Program*, 1994, Version 2.2, Bruker AXS, Madison, Wisconsin, USA; (b) Sheldrick, G. M. SHELXTL, *Structure Determination and Refinement Programs*, 1999, Version 5.1 Bruker AXS, Madison, Wisconsin, USA.
10. The molecular modelling illustrated in Figs. 2 and 3 was performed on a Power Computing PowerCenter Pro with a 604e RISC processor running at 210 MHz and using the modified MM2 force field implemented in Chem3D Pro version 3.5.1 from CambridgeSoft. Initial structures for the Monte Carlo conformational searches were generated by a custom written Applescript which forced the random rotation of selected torsional angles, prior to crude energy minimisation, filtering and final minimisation of low energy conformations. Further modelling on a Silicon Graphics workstation using XED-98[11] also indicated that the all-axial chair conformation was the global minimum for **5** with the *N*-benzhydryl auxiliary (the all-equatorial chair conformation being around 3 kcal/mol higher in energy), whilst the *N*-benzyl derivative prefers the all-equatorial conformation; these studies revealed a relatively small energetic penalty for placing the *N*-auxiliary also axial, as is observed in the crystal structure of **7**.
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