Tetrahedron Letters 49 (2008) 5986–5989

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formal Alder-ene reaction of a bicyclo[1.1.0]butane in the synthesis of the tricyclic quaternary ammonium core of daphniglaucins

Masafumi Ueda[†], Maciej A. A. Walczak, Peter Wipf[*]

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

ARTICLE INFO

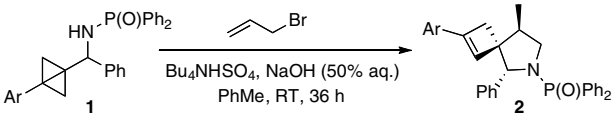
Article history:
Received 4 July 2008
Accepted 29 July 2008
Available online 5 August 2008

ABSTRACT

A tricyclic substructure of the tetracyclic nitrogen core of the daphniglaucins was formed by an oxidative activation of the allyl side chain of a bicyclo[1.1.0]butylmethylamine, a spontaneous intramolecular formal Alder-ene reaction, and a selective cyclization of a triol intermediate.

Among complex alkaloids, quaternary ammonium salts occupy a unique position because of their frequently intricate architecture. Some of these compounds are used medicinally as anticancer and antimicrobial agents,[1] and they have also found utility as chiral phase transfer catalysts.[2] These polycyclic alkaloids constitute challenging targets for natural product total synthesis (Fig. 1).[3] For example, the daphniglaucins are cytotoxic quaternary *Daphniphyllum* alkaloids isolated in 2003 by Kobayashi et al. from the leaves of *Daphniphyllum glaucescens* and have an unusual framework consisting of a novel fused-polycyclic skeleton assembled around a 1-azoniatetracyclo[5.2.2.0.^{1,6}0.^{4,9}]undecane ring system.[3c–e] Despite these attractive structural features, a total synthesis or a partial synthetic approach has not yet been reported.

In this Letter, we describe our studies on the use of a bicyclo[1.1.0]butane building block in the synthesis of the cyclic quaternary ammonium scaffold of daphniglaucins. To the best of our knowledge, this sequence represents the first use of this highly strained hydrocarbon in alkaloid synthesis.[4] We have previously reported on the preparations and ring transformations of bicyclobutylmethylamines.[5,6] An intramolecular ene reaction of N-allylated derivatives of **1** provides a stereoselective access to spirocyclic pyrrolidines **2** under remarkably mild phase transfer conditions (Scheme 1).



Scheme 1. Cascade N-allylation/formal Alder-ene sequence.

In the continuation of our explorations of the novel intramolecular cycloaddition chemistry of bicyclo[1.1.0]-butanes,[5,6] we intended to demonstrate their utility for the synthesis of biologically interesting cyclic quaternary ammonium salts. We envisioned that a tricyclic substructure of the core heterocycle of daphniglaucin A, that is, the 1-azoniatricyclo[5.2.2.0^{5}]undecane **3**, could be derived from a triol **4**, which could be obtained from spirocycle **5** via oxidative cleavage and reduction (Scheme 2). An intramolecular formal Alder-ene reaction of bicyclobutylmethylamine **6** would produce **5**. The aldehyde group in the nitrogen side

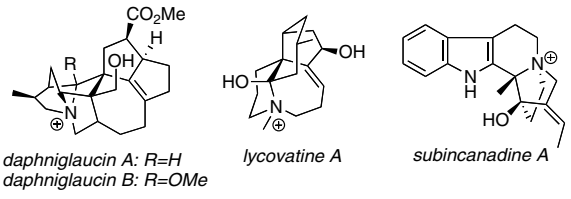
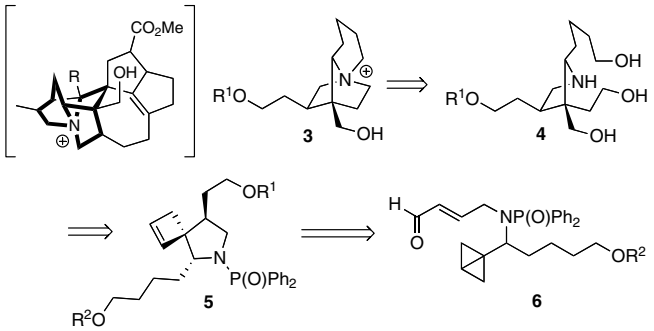


Figure 1. Representative polycyclic quaternary alkaloids.



Scheme 2. Retrosynthetic strategy toward cyclic quaternary ammonium salts from bicyclobutanes. The corresponding core structure of daphniglaucins is highlighted.

* Corresponding author. Tel.: +1 412 624 8606; fax: +1 412 624 0787.
E-mail address: pwipf@pitt.edu (P. Wipf).
† Present address: Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan.

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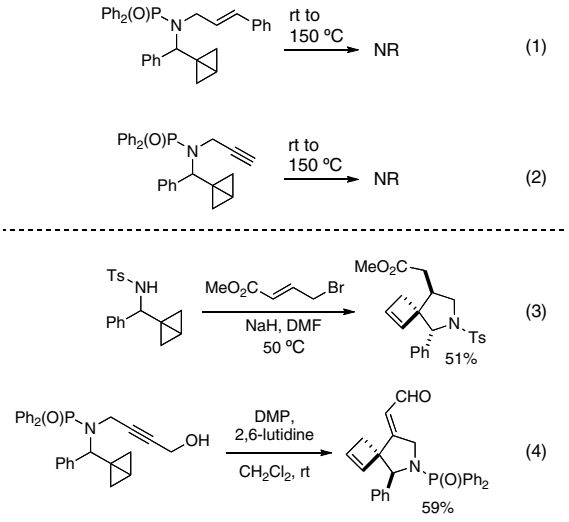
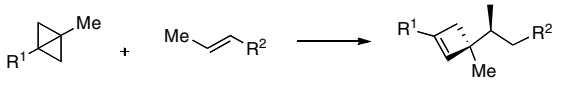
doi:10.1016/j.tetlet.2008.07.179



Scheme 3. Formal Alder-ene reactions of terminally unsubstituted bicyclobutylmethylamines require electron-deficient enophiles.

Table 1
Frontier molecular orbital calculations of the HOMO–LUMO gap[a] as a function of R^1 and R^2 substituents on ene and enophile



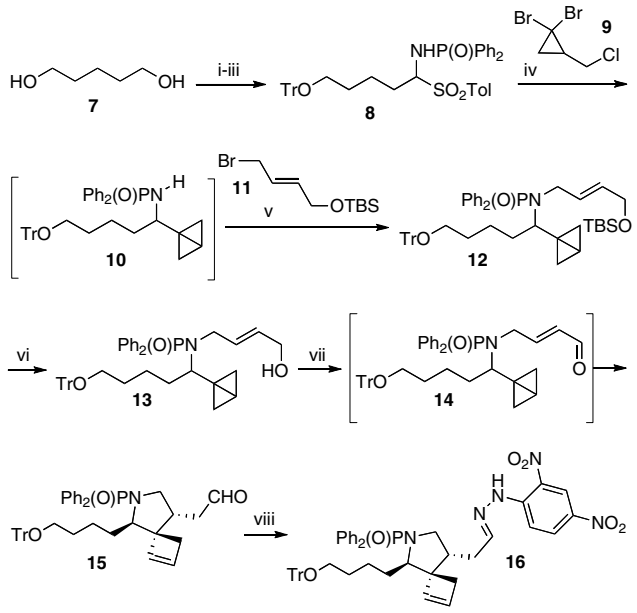
Entry	R^1	HOMO of bicylobutane (eV)	R^2	LUMO of alkene (eV)	ΔE (LUMO–HOMO) (eV)
1	Ph	−7.95	H	5.25	13.20
2	H	−9.37	H	5.25	14.62
3	CHO	−9.73	H	5.25	14.98
4	H	−9.37	CHO	2.95	12.32

[a] Calculated with a HF/6-31G* basis set using MACSPARTAN 06.

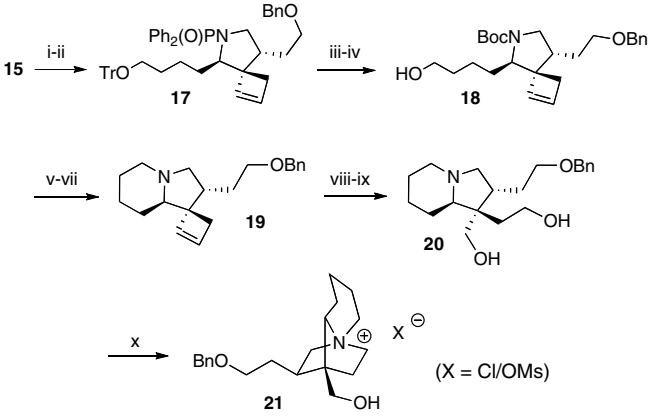
chain in **6** was found to be essential for the thermal ene reaction of bicyclo[1.1.0]-butanes lacking conjugated aromatic substituents. The need for an electron-poor enophile in this process was supported by preliminary experimental as well as theoretical studies (Scheme 3 and Table 1).

Even upon heating unactivated allylic and propargylic bicyclobutylmethylamines to 150 °C, only starting material was isolated (Scheme 3, Eqs. 1 and 2). More vigorous conditions led to decomposition, but ene-products could not be identified. In contrast, an electron-deficient ester function provided the cycloaddition product in 51% yield at 50 °C (Scheme 3, Eq. 3). In situ oxidation of a propargyl alcohol to the ynal with Dess-Martin periodinane (DMP) led to the analogous cycloaddition product at room temperature and in good yield (Scheme 3, Eq. 4).

Table 1 provides an overview of HOMO–LUMO energies calculated at the HF/6-31G* level for substituted enophiles and bicyclobutanes. In order to minimize the HOMO–LUMO gap, the ene reaction is expected to proceed via the interaction of the HOMO of the bicyclobutane with the LUMO of the alkene. A large frontier orbital energy difference was observed between electron-rich alkenes and terminal bicyclobutanes or electron deficient bicyclobutanes bearing a formyl group (entries 2 and 3). In contrast, a phenyl substituent on the bicyclobutane or a carbonyl substituent at the alkene considerably enhances the reactivity by diminishing the HOMO–LUMO gap by ca. 1.4 and 2.3 eV, respectively (entries 1 and 4). In practice, all intramolecular ene reactions that we attempted with analogs of **6** that did not contain an electron-withdrawing aldehyde or ester function on the allylic amide side chain failed under the classical thermal conditions.



Scheme 4. Reagents and conditions: (i) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 71%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 92%; (iii) $H_2NP(O)Ph_2$, *p*-$TolSO_2H$, Et_2O, rt, 94%; (iv) MeLi, *t*-BuLi, Et_2O, THF, −78 °C; **8**; (v) Bu_4NHSO_4, 50% aq NaOH, toluene, rt, 58% (2 steps); (vi) TBAF, THF, rt, 85%; (vii) TPAP, NMO, CH_2Cl_2, benzene, rt to reflux, 67% (6:1 dr); (viii) 2,4-dinitrophenylhydrazine, MeOH, rt, 86%.



Scheme 5. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 79%; (ii) BnBr, KOH, 18-crown-6, THF, H_2O, rt, 86%; (iii) concd HCl, THF, rt; (iv) $(Boc)_2O$, $NaHCO_3$, MeCN, H_2O, rt, 69% (2 steps); (v) MsCl, Et_3N, CH_2Cl_2, rt; (vi) TFA, CH_2Cl_2, rt; (vii) Et_3N, MeCN, rt, 75% (3 steps); (viii) OsO_4, $NaIO_4$, 2,6-lutidine, *t*-BuOH, H_2O, rt; (ix) $NaBH_4$, MeOH, rt, 45% (2 steps); (x) MsCl, $NaHCO_3$, CH_2Cl_2, H_2O, rt, 61%.

The synthesis of an appropriately substituted 1-azoniatricyclo[5.2.2.0^{1,6}]undecane segment of daphniglaucin is outlined in Schemes 4 and 5. 1,5-Pentanediol (**7**) was selectively O-tritylated, oxidized to the aldehyde and then condensed with *N,N*-diphenylphosphinamide in the presence of *p*-toluenesulfinic acid to afford the imine precursor **8**.[7,8] Treatment of 1,1-dibromo-2-chloromethylcyclopropane (**9**) with MeLi followed by *t*-BuLi generated bicyclo[1.1.0]butan-1-yllithium in situ,[9] which, upon addition of **8**, eliminated the sulfinylate and added to the resulting imine to give amide **10**. This labile 1,2-adduct was immediately subjected to N-alkylation with allylbromide **11**[10] under phase-transfer conditions to give bicyclobutane **12** in 58% overall yield from **8**. Desilylation of

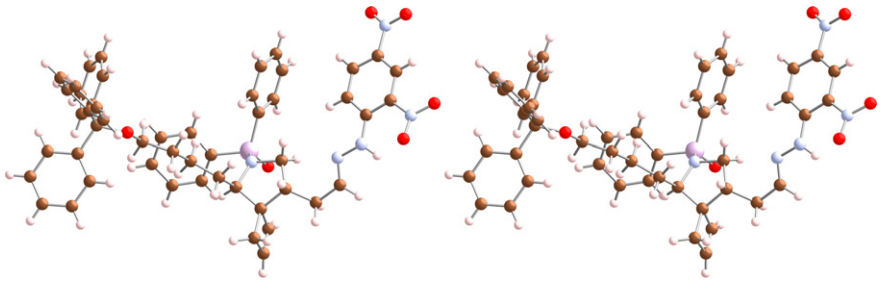


Figure 2. Stereoview of the X-ray crystal structure of hydrazone **16**.

12 with TBAF afforded the allylic alcohol **13**. Several oxidants, solvents, and reaction temperature conditions were examined in our attempts to optimize the conversion of **13** to **14**. The best result was obtained when TPAP in DCM was used as the oxidant at room temperature for 1 h; aldehyde **14** was not isolated from the reaction mixture but was immediately heated after the addition of benzene as a cosolvent, thus affording the formal ene product **15** in 67% yield as a 6:1 mixture of diastereomers.[11–13] The major isomer was isolated by chromatography on SiO_2, and its relative configuration was secured by an X-ray structure analysis of the hydrazone derivative **16** (Fig. 2).[5b]

The major diastereomer **15** was used in the subsequent transformation to the quaternary ammonium salt **21** (Scheme 5). Reduction of the aldehyde with $NaBH_4$ and protection of the resulting alcohol with BnBr provided benzyl ether **17**. We determined empirically that the best strategy for formation of the tricyclic ammonium ion was to close the fused six-membered ring before installing the second, bridged six-membered ring. Accordingly, **17** was converted to the primary alcohol **18** by concurrent solvolysis of *N,N*-diphenylphosphinoyl and trityl groups, followed by *N*-Boc protection. Mesylation of the primary hydroxyl group of **18**, cleavage of the Boc group with TFA, and cyclization in the presence of triethylamine furnished indolizidine **19**. Oxidative ring opening of the cyclobutene was readily accomplished by a Johnson–Lemieux oxidation in the presence of 2,6-lutidine, and the resulting dialdehyde was reduced to diol **20** with $NaBH_4$.[14] Finally, double mesylation of diol **20** with excess MsCl in $NaHCO_3/H_2O$/DCM resulted in spontaneous cyclization followed by in situ hydrolysis of the unreacted neopentyl mesylate to give the tricyclic quaternary ammonium salt **21**.[15,16] Target compound **21** was isolated as an approximately 4:1 mixture of chloride and mesylate salts based on ^{1}H NMR integration of the mesylate methyl group.

In conclusion, we have successfully extended the utility of the bicyclobutane strained ring system to alkaloid synthesis. The key reaction for the construction of the tricyclic quaternary ammonium core of daphniglaucin was based on the thermal intramolecular formal Alder-ene reaction of the N-allylated bicyclo[1.1.0]butylmethylamine **14**. Further studies toward the total synthesis of daphniglaucins and other applications of bicyclobutanes in target-directed synthesis are currently in progress in our laboratories.

Acknowledgments

This work was supported in part by NIH Grant P50-GM067082 and Merck Research Laboratories. We thank Dr. Steve Geib for an X-ray crystallographic analysis. M.U. is grateful for the support from Hyogo Science and Technology Association.

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11. *Experimental protocol for the formation of* **15** *from* **13**: TPAP (96 mg, 0.27 mmol) was added to a stirred solution of alcohol **13** (1.8 g, 2.7 mmol), powdered 4 Å sieves (2 g) and 4-methylmorpholine N-oxide (651 mg, 5.39 mmol) in CH_2Cl_2 (30 mL) at rt. The reaction mixture was stirred for 1 h at rt, diluted with benzene (200 mL), heated at reflux for 4 h and filtered through a thin pad of Celite. The filtrate was concentrated and purified by chromatography on SiO_2 (AcOEt) to afford a diastereomeric mixture (6:1) of spirocycles (1.21 g, 67%) as a colorless foam, which was carefully re-purified by chromatography on SiO_2 (AcOEt) to give the major isomer **15** (942 mg, 52%).
12. *Spectral data of* **15**: IR (neat) 3413, 3057, 2937, 2869, 1723, 1489, 1439, 1190, 1121, 1073, 1047, 909, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.95–7.88 (m, 2H), 7.78–7.71 (m, 2H), 7.54–7.20 (m, 21H), 6.47 (d, J = 3.0 Hz, 1H), 6.11 (d, J = 3.0 Hz, 1H), 3.52–3.37 (m, 2 H), 3.30–2.78 (m, 4H), 2.58 (dd, J = 18.0, 3.0 Hz, 1H), 2.45 (d, J = 13.5 Hz, 1H), 2.44–2.38 (m, 1H), 2.22 (d, J = 13.5 Hz, 1H), 1.93–1.76 (m, 1H), 1.55–1.18 (m, 4H), 1.02–0.88 (m, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 201.4, 144.3, 141.2, 134.5, 133.0, 132.8 (d, J = 9.0 Hz), 132.2 (d, J = 9.8 Hz), 131.7 (d, J = 2.3 Hz), 131.4 (d, J = 3.0 Hz), 131.3, 131.1, 128.6, 128.4, 128.2, 128.1, 127.7, 126.7, 86.2, 64.2, 63.1, 59.7 (d, J = 1.5 Hz), 50.3, 44.5, 33.7 (d, J = 4.5 Hz), 34.7, 33.8 (d, J = 5.3 Hz), 29.9, 23.8; MS (ESI) m/z (rel intensity) 688 ([M+Na]$^+$, 90), 527 (25), 443 (37), 243 (100); HRMS (ESI) calcd for $C_{44}H_{44}NO_3PNa$ (M+Na) 688.2957, found 688.2964.
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15. *Experimental protocol for the formation of* **21** *from* **20**: To a solution of diol **20** (18 mg, 0.054 mmol) in CH_2Cl_2 (3 mL) were added $NaHCO_3$ (10 mg, 0.12 mmol), H_2O (0.12 mL) and MsCl (0.009 mL, 0.12 mmol) at 0 °C. The reaction mixture was stirred for 5 h at rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and an insoluble solid was removed by filtration. After the solvent was evaporated under reduced pressure, the residue was dissolved in water. The solution was filtered through a small pad

of Celite and the filtrate was concentrated in vacuo to form white solid, which was recrystallized in CH_2Cl_2 and hexane to afford the ammonium salt **21** (12 mg, 61%) as a 4:1 mixture of Cl^- and MsO^- counterions.

16. *Spectral data of* **21**: White solid; IR (neat) 3224, 2932, 2844, 1452, 1360, 1195, 1171, 1098, 1072, 740 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.37–7.29 (m, 5H), 5.60–5.10 (br, 1H), 4.47, 4.44 (AB, J = 12.0 Hz, 2H), 3.84 (t, J = 11.5 Hz, 1H), 3.75 (t, J = 8.5 Hz, 1H), 3.62 (d, J = 11.5 Hz, 1H), 3.53 (d, J = 11.5 Hz, 1H), 3.52 (t, J = 11.5 Hz, 1H), 3.45–3.23 (m, 5H), 3.19–3.12 (m, 1H), 2.34 (s, 0.6H, $CH_3SO_3^-$)), 2.18–2.11 (m, 1H), 2.08 (td, J = 12.0, 5.5 Hz, 1H), 1.98–1.91 (m, 1H), 1.84–1.66 (m, 5H), 1.63–1.55 (m, 1H), 1.51 (q, J = 11.5 Hz, 1H), 1.41–1.29 (m, 1H); ^{13}C NMR (75 Hz, CD_3OD) δ 139.8, 129.6, 129.1, 128.9, 74.4, 74.0, 71.2, 69.5, 60.8, 55.4 (2C), 54.2, 41.6, 32.1, 31.7, 22.3, 21.8, 20.7; MS (ESI) *m/z* (rel. intensity) 316 ($[M-Cl]^+$ or $[M-OMs]^+$, 100), 224 (30); HRMS (ESI) calcd for $C_{20}H_{30}NO_2$ (M−Cl or M−OMs) 316.2277, found 316.2265.