Formal Total Synthesis of (±)-Conduramine E Utilising the Bryce-Smith–Gilbert Photoamination Reaction

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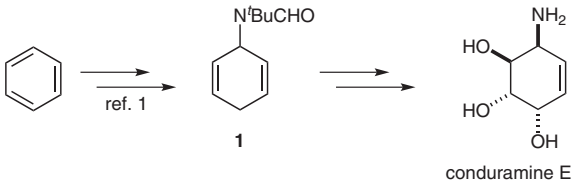
Dedicated to Prof. Gerry Pattenden in celebration of his 70th birthday

Abstract: Utilising a Bryce-Smith–Gilbert photoamination of benzene as a key step, a synthesis of (±)-conduramine E was carried out. A highly regioselective dihydroxylation of a cyclic diene was effected utilising Sharpless AD-mix-β.

Key words: Bryce-Smith–Gilbert photoamination, (±)-conduramine E, diastereocontrolled synthesis

We have recently reported on the use of formamide **1**, prepared via Bryce-Smith–Gilbert photoamination of benzene, as a precursor for the enantioselective synthesis of (–)-fortamine.[1,2] The synthetic potential of this crystalline compound has now been further realized, forming the foundation for a synthesis of (±)-conduramine E (Scheme 1).[3]

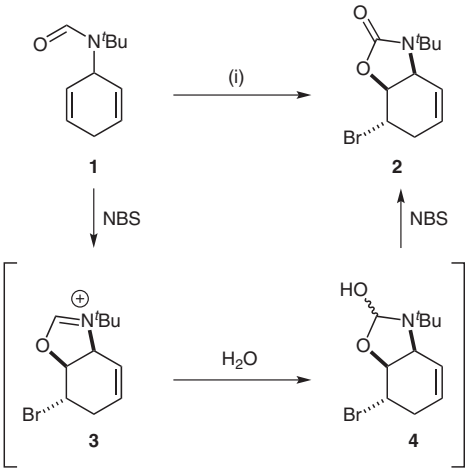


Scheme 1 Proposed synthesis of conduramine E

Thus, beginning from formamide **1**,[1] bromonium ion induced cyclisation was investigated to install the relative stereochemistry between the adjacent carbon–nitrogen and carbon–oxygen bonds required for conduramine E. However, contrary to expectation, treatment of **1** with two equivalents of *N*-bromosuccinimide (NBS) delivered a 49% yield of oxazolidinone **2**, presumably via hydration of the intermediate **3** and oxidation of **4** (Scheme 2).

In an effort to improve the yield of this conversion we examined a two-step procedure (Scheme 3). Initial treatment of **1** with polymer-supported Br_3^- afforded formate **5**, presumably again via **4**.[4] It is proposed that the acidic nature of this reagent is sufficient to cause N-protonation of **4**, driving its ring opening to give **5**. It is noteworthy that, in the presence of 2,6-lutidene, amidinium ion **7** was isolated, presumably via **6**. The structure of **7** was confirmed by X-ray crystallographic analysis.[5] In the absence of protonation, **4** would be expected to rearrange to the thermodynamically more stable formamide **6** with subsequent cyclization to afford **7**.[6] Overall, this transformation achieves the same stereochemical outcome as a Woodward–Prevost dihydroxylation.[7] Hydrolysis of the formate **5** afforded an amino alcohol that was directly protected with triphosgene to give the desired urethane **2** in an overall, purified yield of 86% from **1**.

Treatment of **2** with DBU effected elimination of HBr to afford diene **8** in 90% yield (Scheme 4). At this stage, synthesis of conduramine E required a regio- and stereoselective dihydroxylation to give **9**. Treatment of **8** under modified Van Rheenen conditions resulted in dihydroxylation exclusively on the *exo* face with a 4:1 mixture of regioisomers (**9**/**10**) in 55% combined yield.[8] Sharpless asymmetric dihydroxylation reagents are usually ineffective at kinetic resolution but can be regioselective in diene dihydroxylation.[9] Indeed, when we treated **8** with AD-mix-β for five hours between 0 °C and –5 °C, **9** was obtained as a single regio- and stereoisomer in 76% yield.[10] The shape of the bicyclic ring system makes the *exo* stereoselectivity unsurprising but the high regioselectivity is more difficult to rationalise. Unfortunately, kinetic resolution was ineffective with only 18% ee being achieved at 40% conversion with AD-mix-β.



Scheme 2 Oxidative cyclisation of **1**. *Reagents and conditions*: (i) NBS (2 equiv), CH_2Cl_2, 0 °C (49%).

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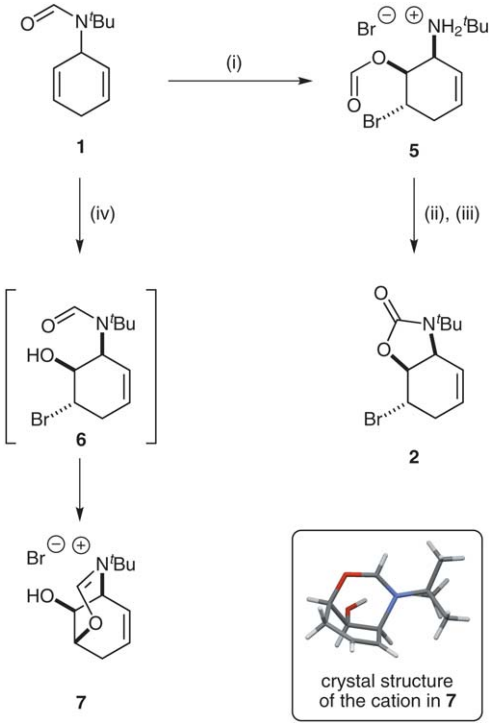
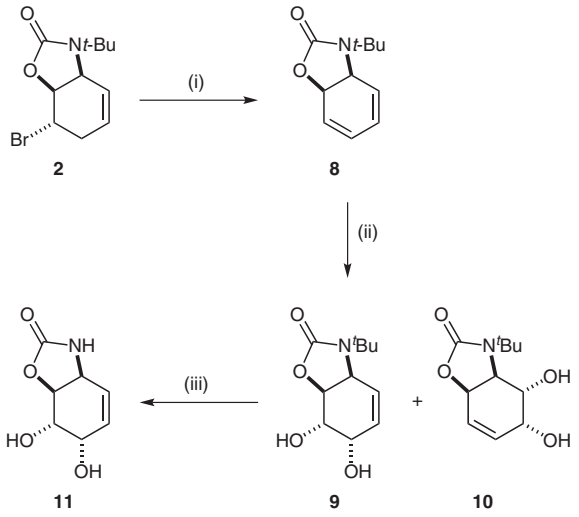
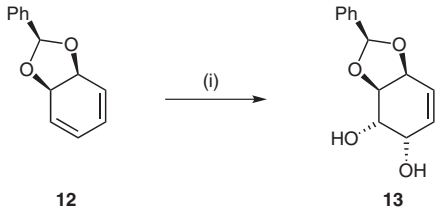


Scheme 3 Optimised synthesis of **2**. *Reagents and conditions*: (i) polymer-supported Br_3^-, CH_2Cl_2, r.t.; (ii) 1 M HCl–MeOH; (iii) triphosgene, pyridine, CH_2Cl_2, (86% from **1**); (iv) polymer-supported Br_3^-, 2,6-lutidene, CH_2Cl_2, r.t. (68%).



Scheme 4 Regio- and stereoselective dihydroxylation of **8**. *Reagents and conditions*: (i) DBU (1.6 equiv), toluene, r.t. (90%); (ii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1) (76%) (**9**/**10** = 100:0) or $K_2OsO_4{\cdot}2H_2O$, NMO, H_2O–acetone–*t*-BuOH (1.0:0.75:1.0) (55%, **9**/**10** = 4:1); (iii) TFA, reflux (76%).

During a study directed toward the synthesis of (+)-conduritol E, the *meso*-diene **12** was effectively desymmetrised to give **13** (85% ee) by treatment with AD-mix-β whilst, as expected, AD-mix-α afforded its enantiomer (Scheme 5).[9,11]



Scheme 5 Takano's desymmetrisation of **12**. *Reagents and conditions*: AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1, 85%).

To examine the effect of the cinchona alkaloid ligand on the outcome of the dihydroxylation of **8**, its reaction with AD-mix-α was carried out but the same product (**9**) was obtained (68% yield). Thus, as suggested by the reaction under Van Rheenen conditions, the selectivity is innate to the structure of **8**. Calculating the transition state energies in the *exo* approach of OsO_4–NH_3, as a model, to either double bond of **8** showed that leading to **9** to be 0.9 kcal mol^{-1} lower in energy than that leading to **10** (Figure 1). Whilst no firm conclusions can be made on the basis of this small difference in energies, it is consistent with the observed ratio of products obtained in the room-temperature Van Rheenen dihydroxylation.[12]

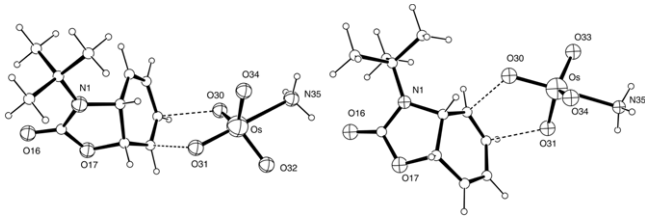


Figure 1 Calculated transition-state models leading to **9** and **10** (Gaussian 03); DFT used with B3LYP. LANL2DZ basis set for Os, 6-31+G* for other atoms.

Deprotection of **9** was effected by refluxing with TFA to afford **11** in 76% yield,[13,14] which has been previously reported by Prinzbach et al. as an intermediate in their synthesis of (–)-conduramine E.[3a] For completeness, utilising known conditions, **11** was hydrolysed with $Ba(OH)_2$ to give conduramine E then converted into its tetraacetyl derivative and its ^1H NMR spectrum found to be in accord with data reported by Chida et al.[3b]

In conclusion, we have further demonstrated the synthetic utility of crystalline formamide **1**, obtained by photoamination of benzene, as a precursor for the regio- and diastereocontrolled synthesis of natural products possessing polyhydroxylation.

Acknowledgment

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References and Notes

(1) (a) Gibson, S. *PhD Thesis*; University of Reading: UK, **2004**. (b) **Synthesis of 1**
A solution of *N-tert*-butylcyclohexa-2,5-dienylamine contaminated with *N-tert*-butylcyclohexa-2,4-dienylamine (2.5 g, 16.5 mmol)[2b] and Et_3N (4.65 mL, 33.4 mmol, 2 equiv) in dry Et_2O (375 mL) was stirred under argon at 0 °C before formic acetic anhydride (1.75 mL, 19.8 mmol, 1.2 equiv) was added slowly, and the resulting yellow solution left stirring for 4 h whilst allowing to warm to r.t. The reaction was quenched with H_2O and the layers separated. The aqueous layer was extracted with Et_2O (3 × 150 mL), the combined organic extracts dried over $MgSO_4$, and the solvent removed in vacuo. The resultant amber oil was purified via flash column chromatography (Florisil®, gradient; hexane–EtOAc = 19:1 to 2:1) to give *N-tert*-butyl-*N*-cyclohexa-2,5-dienylformamide (**1**) as a colourless crystalline solid (1.83g, ca. 62%); mp 44–47 °C; R_f = 0.11 (SiO_2, hexane–EtOAc = 7:3). IR (thin film): ν_{max} = 3030, 2972, 2814, 1668 (C=O stretch), 1220. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 [9 H, s, $C(CH_3)_3$, rotamer A], 1.48 [9 H, s, $C(CH_3)_3$, rot. B], 2.64–2.69 [2 H, m, H(4), rot. A and B], 4.56–4.63 [1 H, m, H(1), rot. A], 4.80–4.95 [1 H, m, H(1), rot. B], 5.57–5.91 [4 H, m, 2 × C*H*=C*H*, rot. A and B], 8.16 [1 H, s, C(O)H, rot. B], 8.51 [1 H, s, C(O)H, rot. A], [rot. A/rot. B = 2:1]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.95, 26.39 [CH_2, C(4), rots. A and B], 29.33 [CH_3, $C(CH_3)_3$, rot. B], 29.71 [CH_3, $C(CH_3)_3$, rot. A], 48.07, 49.02 [CH, C(1), rot. A and B], 56.96, 57.24 [C, $C(CH_3)_3$, rot. A and B], 126.28, 126.41, 126.93, 127.86 [CH, C(2,3,5,6), rot. A and B], 162.72 [C, *C*(O)H, rot. A], 165.89 [C, *C*(O)H, rot. B]. HRMS (CI): *m/z* calcd for $C_{11}H_{17}NO$ [M^+]: 179.1310; found: 179.1310. Anal. Calcd (%) for (CHN): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.46; H, 9.68; N, 7.67.

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(5) **Crystal Data**
$C_{11}H_{20}BrNO_3$, *M* = 294.19, monoclinic, *Z* = 4, spacegroup $P2_1/a$, *a* = 11.297 (14) Å, *b* = 9.511 (11) Å, *c* = 13.553 (14) Å, *β* = 106.50 (1)°, *U* = 1396 (3) Å^3. 2765 data were collected with MoKα radiation at 150 K using the Oxford Diffraction X-Calibur CCD System. The crystal was positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10 s. Data analysis was carried out with the CrysAlis program.[15] The structure was solved using direct methods with the Shelxs97 program.[16] The nonhydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. An absorption correction was applied using ABSPACK.[17] The structure was refined on F^2 using Shelxl97 [2] to $R1 = 0.0903$, $wR2 = 0.1744$ for 872 reflections with $I > 2\sigma(I)$. Details of the structure have been deposited at the Cambridge Crystallographic Data Centre as CCDC 752251.

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(10) **Procedure**
AD-mix-β [$K_3Fe(CN)_6$ (0.35 g, 1.08 mmol, 3 equiv), K_2CO_3 (0.16 g, 1.08 mmol, 3 equiv), $(DHQD)_2PHAL$ (2.5 mol%) and $K_2OsO_4 \cdot 2H_2O$ (2.5 mol%)] were dissolved in *t*-BuOH–H_2O (1:1; 20 mL) and stirred for 5 min before addition of $MeSO_2NH_2$ (29 mg, 0.36 mmol, 1 equiv). The solution was cooled to 0 °C before addition of (±)-(3a*S*,7a*R*)-3-(*tert*-butyl)-3,3a,7a-trihydrobenzoxazol-2-one (**8**, 70 mg, 0.36 mmol) in *t*-BuOH (1 mL). The reaction was left stirring for 5 h between 0 °C and –5 °C. The reaction was diluted with MeOH and evaporated to dryness in vacuo. The residue was dissolved in $CHCl_3$–MeOH (9:1) and filtered through a plug of Celite® upon silica gel. The filtrate was concentrated in vacuo to give the crude diol which was purified by flash chromatography (SiO_2, $CHCl_3$–MeOH = 9:1) to yield (±)-(3a*S*,6*S*,7*S*,7a*S*)-3-(*tert*-butyl)-6,7-dihydroxy-3,6,7,3a,7a-pentahydrobenzoxazol-2-one (**9**) as a colourless oil that solidified on standing (63 mg, 76%); mp 63–65 °C; R_f = 0.17 (SiO_2, $CHCl_3$–MeOH = 19:1). IR ($CHCl_3$): ν_{max} 3441 (OH stretch), 1728 (C=O stretch) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 [9 H, s, -C(CH_3)$_3$], 3.10 (1 H, br s, OH), 3.54 (1 H, d, *J* = 7 Hz, OH), 4.24–4.27 [2 H, m, H(3a,7)], 4.37–4.40 [1 H, m, H(6)], 4.56–4.61 [1 H, m H(7a)], 5.75 [2 H, br s, H(4,5)]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.79 [-C(*C*H_3)$_3$], 52.52 [CH, C(3a)], 54.37 [C, $C(CH_3)_3$], 64.25 [CH, C(6)], 67.51 [CH, C(7)], 73.47 [CH, C(7a)], 124.87 [CH, C(4)], 131.60 [CH, C(5)], 156.43 (C, C=O). MS (CI): *m/z* (%) = 228 (37) [MH^+]. HRMS: *m/z* calcd for $C_{11}H_{18}NO_4$: 228.1236; found: 228.1242.

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