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Tetrahedron Letters 44 (2003) 7731–7733

TETRAHEDRON LETTERS

Synthesis of natural (–)-hamigeran B

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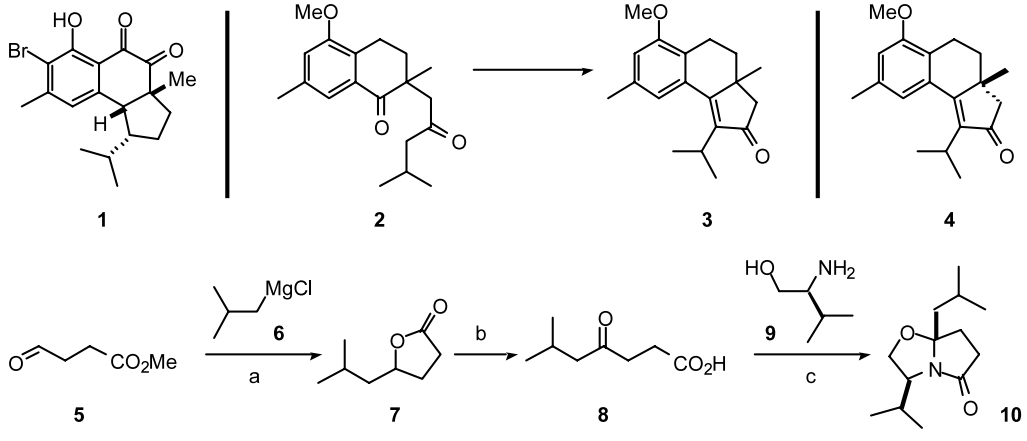
Received 8 August 2003; revised 20 August 2003; accepted 21 August 2003

Abstract—Alkylation of lactam **10**, first with iodide **15** and then with MeI, gave mainly (18:1) lactam **18**. This was converted by treatment with *t*-BuLi and then with aqueous base into enone **4**, which was elaborated into (–)-hamigeran B. A key feature of the last part of the synthesis is the use of *t*-BuMe$_2$Si-groups (as in intermediate **24**) both to direct hydrogenation from the appropriate face and to protect the benzylic C–O bond from hydrogenolysis.

The hamigerans are a small group of structurally related and unusual natural products that were isolated[1] from a marine sponge. Several hamigerans show in vitro antitumor activity (IC_{50} values of 8–74 μM), but the most notable characteristic would seem to be the fact that (–)-hamigeran B (**1**) strongly[1,2] inhibits both herpes and polio viruses, with only slight cytotoxicity. The absolute stereochemistry shown for **1** was suggested on the basis of structural analogy to another hamigeran for which the assignment was made by X-ray analysis.[1] Synthesis of the hamigerans presents some complex stereochemical problems; these were first solved[3] by the Nicolaou group, who described routes to several members of the family, including **1**.[4] We have recently found[5] an efficient route to racemic hamigeran B; here we describe the application of our method to the synthesis of the optically pure material (–)-hamigeran B (**1**), having the indicated absolute configuration.

As reported previously,[5] our route to (±)-**1** is based on enone **3**, as a key intermediate. This was prepared by base-induced cyclization of the racemic diketone **2**. For synthesis of (–)-hamigeran B, the enantiomer **4** is required; the asymmetric quaternary center would be expected to retain its integrity under the conditions used to elaborate **3**.

Our route to **4** is based on Meyers' method,[6] and required the specific lactam **10** (Scheme 1) and the halide **15** (Scheme 2). The former was readily assembled from aldehyde ester **5**[7] (Scheme 1). Reaction with



Scheme 1. *Reagents and conditions*: (a) **6**, Et_2O, –78°C, 12 h; (b) AcOH, H_2SO_4, $Na_2Cr_2O_7$, room temperature 10 h, reflux 1 h, ca. 53% from **5**; (c) PhMe, add **9**, reflux 15 h (Dean–Stark apparatus), 75%.

Keywords: hamigeran B; Meyers' lactam; hydrogenolysis; silyl groups.
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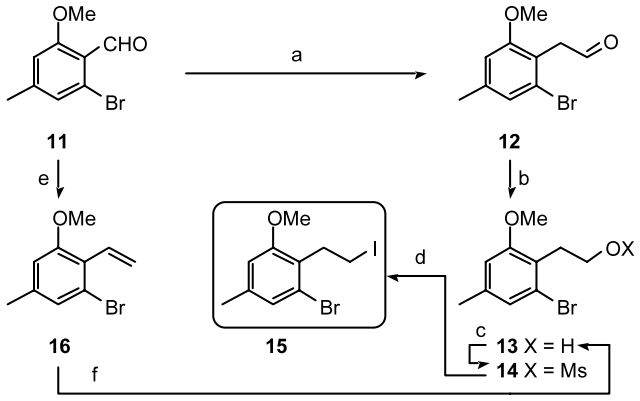
doi:10.1016/j.tetlet.2003.08.089

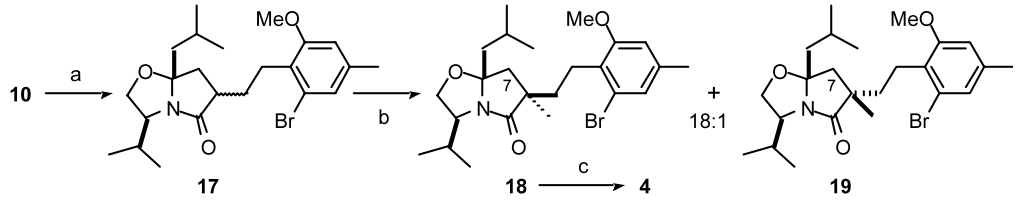


Scheme 2. *Reagents and conditions*: (a) $Ph_3P=CH(OMe)$, PhMe, 0°C, 2 h, then 10% hydrochloric acid, acetone, reflux, 3.5 h, 99%; (b) DIBAL, CH_2Cl_2, 0°C, 30 min, 90%; (c) MsCl, Et_3N, CH_2Cl_2, 0°C, 30 min; (d) NaI, acetone, reflux, 12 h, 92% from **13**; (e) $Ph_3P=CH_2$, PhMe, 0°C, 2 h, 75%; (f) 9-BBN, THF, 0°C, 30 min, room temperature 12 h, then NaOH, H_2O_2, 0°C, 2 h, 87%.

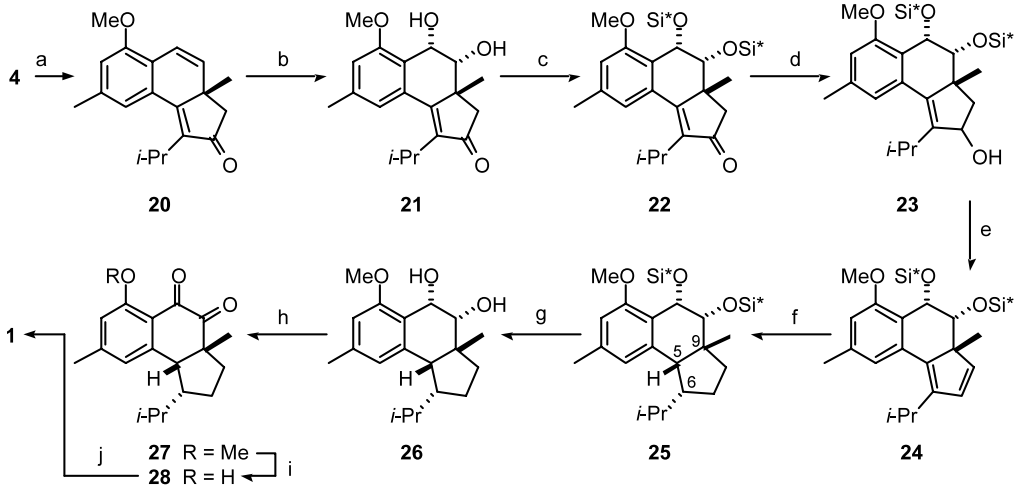
i-BuMgCl (**6**) gave lactone **7**[8] (which was not obtained pure), and oxidation[9] of the lactone with $Na_2Cr_2O_7$ in aqueous AcOH–H_2SO_4 then afforded keto acid **8**[10] in 54% yield from **5**. Finally, condensation with (*S*)-valinol[11] (**9**) produced[12] the required lactam **10**.

The second component (**15**) was made as summarized in Scheme 2. Aldehyde **11**[13] was homologated (**11**→**12**) by Wittig reaction with $Ph_3P=CH(OMe)$ and acid hydrolysis of the resulting enol ethers (99% over two steps). Reduction (DIBAL-H, 90%) then afforded alcohol **13**. The same compound could be obtained in slightly lower yield by Wittig olefination (**11**→**16**, 75%), followed by hydroboration (9-BBN, then NaOH, H_2O_2, 87%). Conversion of alcohol **13** into its mesylate (MsCl, Et_3N) and displacement of the leaving group by iodide (NaI, acetone) gave the required iodide **15** (92% from **13**).

Alkylation of **10** with **15** (Scheme 3), which required a prolonged reaction time (36 h at room temperature) gave **17** (as a mixture of stereoisomers), and then *endo*[6] methylation (12 h at room temperature) generated the quaternary center, affording **18** and **19** in an 18:1 ratio. The diastereoisomers were separated chromatographically, **18** being obtained pure in 90% yield; the other isomer was not obtained free of starting material (**17**). NOE measurements[17] established that the major product of the alkylation has the stereochemistry shown in **18**. Treatment of **18** with *t*-BuLi, under standard conditions,[6] and in situ hydrolysis, served not only to form the desired tetralone (cf. **2**) but also to



Scheme 3. *Reagents and conditions*: (a) 2 equiv. LDA, THF, HMPA, −78°C, then add **15**, 36 h at room temperature, 79% corrected for recovered **10** (30%), some iodide also recovered; (b) 2 equiv. LDA, THF, HMPA, −78°C, then add MeI, 12 h at room temperature, 95%, 90% yield of **18**; (c) *t*-BuLi, THF, −78°C, 1.75 h, then aqueous $Bu_4NH_2PO_4$ (1 M), reflux 24 h, then NaOH, EtOH, reflux, 24 h, 90%.



Scheme 4. *Reagents and conditions*: Si* = $SiMe_2Bu$-*t*. (a) DDQ, dioxane, reflux, 8.5 h, 74%; (b) OsO_4, NMO, 5:1:4:6 CCl_4–water–*t*-BuOH–acetone, 13 h, 81%; (c) *t*-$BuMe_2SiOSO_2CF_3$, CH_2Cl_2, 2,6-lutidine, 6 h, 73%; (d) DIBAL-H, CH_2Cl_2, 0°C to room temperature, 10 h; (e) MsCl, Et_3N, $ClCH_2CH_2Cl$, room temperature for 30 min, then reflux for 8 h, 84% over two steps; (f) Pd–C, H_2, 39 psi, 1:1 MeOH–hexane, 36 h, 78%; (g) Bu_4NF, THF, reflux, 24 h, 85%; (h) Swern oxidation, 94%; (i) LiCl, DMF, reflux, 20 h, 87%; (j) NBS, *i*-Pr_2NH, CH_2Cl_2, 3 h, 88%.

effect cyclization (cf. **2**→**3**), so that **4** was obtained directly (90%). From this point, the procedures developed for the racemic series were applied without change (Scheme 4). Dehydrogenation of **4** with DDQ gave olefin **20** (74%), and this was subjected to vicinal dihydroxylation (OsO_4, NMO, 81%), which occurred *anti* to the angular methyl group (**20**→**21**). The diol was protected as its bis-*t*-butyldimethylsilyl ether ($BuMe_2SiOSO_2CF_3$, 73%) (**21**→**22**), this choice of protecting groups being essential, as explained previously,[5] in order to control facial selectivity in a later hydrogenation step while preserving the integrity of the benzylic C–O bond, which would otherwise undergo hydrogenolysis. The carbonyl group was then reduced (**22**→**23**, DIBAL-H), and dehydration, achieved by mesylation (MsCl, Et_3N) in $ClCH_2CH_2Cl$ at 0°C to reflux temperature, gave diene **24** (84% over two steps). At this point, hydrogenation (Pd–C, H_2, 39 psi, 1:1 MeOH–hexane) delivered **25** (in 78% yield). Desilylation gave the expected diol (**25**→**26**, Bu_4NF, 85%). The compound was examined by HPLC, using a chiral[18] column. Although baseline separation of the corresponding racemic material was not possible, the trace for the optically active sample showed no sign of a shoulder, and we judge the compound to be optically pure, as expected from the fact that **18** was a single isomer derived from optically pure *S*-valinol. Double Swern oxidation (**26**→**27**, 94%) and demethylation with LiCl in refluxing DMF[19] gave phenol **28** (87%) and, finally, bromination (NBS, *i*-Pr_2NH, 88%)[20] produced (–)-hamigeran B (**1**).[21]

All new compounds, except for **14**, **19**, and **23**, were characterized spectroscopically, including high resolution mass measurement.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support, and Dr. C. Diaper for the HPLC measurements.

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17. The C(7) H in **18** *syn* to the adjacent Me group shows an NOE only to that Me, the other C(7) hydrogen shows NOEs to the CH_2 groups of the ethyl and isobutyl substituents. The C(7) H in **19** *syn* to the adjacent Me group shows NOEs with that Me and with the CH_2 group of the isobutyl substituent, while the other C(7) hydrogen shows NOEs to the CH_2 groups of the ethyl substituent.
18. Chiralcel OD column (0.46×5 cm); eluant 4:1 *i*-PrOH–hexane; flow rate 1.0 mL/min; detection at 230 nm, temperature 25°C; sample concentration ca. 1 mL/mg in MeOH, injection volume 20 μL.
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21. Synthetic **1**: $[\alpha]_D$ –176.4° (*c* 0.142, CH_2Cl_2) [Lit.[1] $[\alpha]_D$ –151.5° (*c* 0.15, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.44 (d, $J=6.5$ Hz, 3H), 0.53 (d, $J=6.6$ Hz, 3H), 1.15–1.23 (m, 1H), 1.28 (s, 3H), 1.49–1.59 (m, 1H), 1.63–1.72 (m, 1H), 1.75–1.85 (m, 1H), 2.25–2.33 (m, 1H), 2.50 (s, 3H), 2.62 (ddd, $J=5.5$, 7.7, 13.1 Hz, 1H), 3.38 (d, $J=9.2$ Hz, 1H), 6.82 (s, 1H), 12.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.7 (q′), 23.3 (q′), 24.3 (q′), 24.4 (q′), 26.7 (t′), 28.1 (d′), 33.8 (t′), 51.3 (d′), 56.2 (q′), 56.9 (s′), 111.5 (s′), 117.2 (s′), 124.2 (d′), 142.7 (s′), 150.2 (s′), 160.8 (s′), 184.4 (s′), 199.0 (s′); exact mass *m*/*z* calcd for $C_{18}H_{21}O_3{}^{79}Br$ 364.06741, found 364.06791. Compound **4**: FTIR ($CHCl_3$, cast) 2957, 1693, 1610 cm^{-1}; $[\alpha]_D=-345.1°$ (*c* 0.304, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3H), 1.19 (d, $J=6.9$ Hz, 3H), 1.37 (d, $J=7.0$ Hz, 3H), 1.66–1.74 (m, 1H), 2.07 (ddd, $J=1.0$, 6.9, 13.2 Hz, 1H), 2.20 (d, $J=18.5$ Hz, 1H), 2.33 (d, $J=18.4$ Hz, 1H), 2.37 (s, 3H), 2.61–2.71 (m, 1H), 2.86 (dd, $J=7.0$, 18.8 Hz, 1H), 3.12 (septet, $J=7.0$ Hz, 1H), 3.83 (s, 3H), 6.70 (s, 1H), 6.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q′), 20.6 (q′), 20.8 (t′), 21.7 (q′), 23.0 (q′), 25.7 (d′), 36.0 (t′), 38.7 (t′), 51.1 (s′), 55.3 (q′), 111.8 (d′), 120.9 (d′), 123.5 (s′), 131.5 (s′), 136.0 (s′), 140.6 (s′), 157.2 (s′), 170.1 (s′), 208.2 (s′); exact mass *m*/*z* calcd for $C_{19}H_{24}O_2$ 284.17764, found 284.17735.