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Stereoselective ring contraction diverts the Mitsunobu reaction of a 6-hydroxy-1,4-diazepan-2-one

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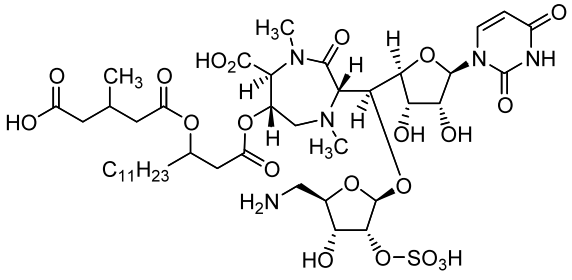
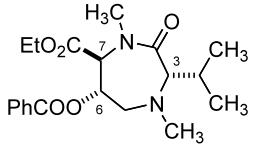
Abstract—Attempted Mitsunobu inversion at C-6 of a 6-hydroxy-1,4-diazepan-2-one led instead to a ring-contracted 1,4-piperazine-2-one by way of transannular participation by N-4. The structure and unusual half-boat conformation of the product were determined by NMR analysis. © 2003 Elsevier Science Ltd. All rights reserved.

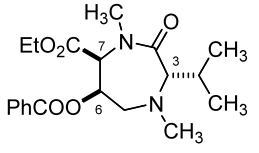
The Mitsunobu reaction is among the most dependable methods for inverting the stereochemistry of a secondary hydroxyl group.[1] Typically, nearby functional groups such as esters, amides, and ethers do not interfere; however, appropriately situated basic amino groups can participate at the carbon center undergoing displacement. In the course of our work on the assignment of the stereochemistry of liposidomycin C (structure shown below), we synthesized, and assigned the relative stereochemistry to, three of the four possible diastereomers of a racemic model system, 6-benzoyloxy-1,4-dimethyl-7-ethoxycarbonyl-3-isopropyl-1,4-diazepan-2-one (e.g. **1**).[2] The missing diastereomer, diazepanone **2**, has the 3*S**,6*R**,7*S** stereochemistry, which is to say that it is epimeric at C-6 with the most readily obtained isomer, **1**. As a means to convert **1** to a model compound with the 3*S**,6*R**,7*S** stereochemistry, we envisioned inverting the hydroxyl group at C-6 by the Mitsunobu reaction. In the most stable conformation (a pseudo-chair[2]), the pseudo-equatorial N-3 lone pair of **1** is poorly positioned to participate at C-6.



liposidomycin C



1 (racemic)



2 (racemic)

Scheme 1 shows the attempted synthesis of **2**. Reduction of the two ester groups of **1** with lithium borohydride in refluxing THF solution[3] gave the desired diol **3**, as well as an over-reduced alcohol, **4**. The latter product might arise by elimination of benzoic acid from C-6,7, followed by in situ hydroboration,[4] although alternative pathways involving N-4 participation are also possible. Selective silylation at the primary hydroxyl group of **3** was achieved with *tert*-butylchlorodiphenylsilane,[5,6] and the resulting secondary alcohol **5** was subjected to Mitsunobu reaction conditions (diethyl azodicarboxylate, triphenylphosphine, and benzoic acid) in benzene solution. A single higher-R_f benzoate was isolated in good yield. Spectroscopic analysis, however, indicates that the product is not the expected inverted diazepanone benzoate, but rather the isomeric ring-contracted piperazinone **6**.

Whereas ^{1}H and ^{13}C NMR spectra revealed the presence of a primary benzoate and primary silyl ether, the stereochemistry and conformation at C-5 and C-6 of **6** remained ambiguous. A product featuring *trans*-diaxially disposed H-5 and H-6 can be ruled out because of the small H-5/H-6 coupling constant (3.6 Hz upon

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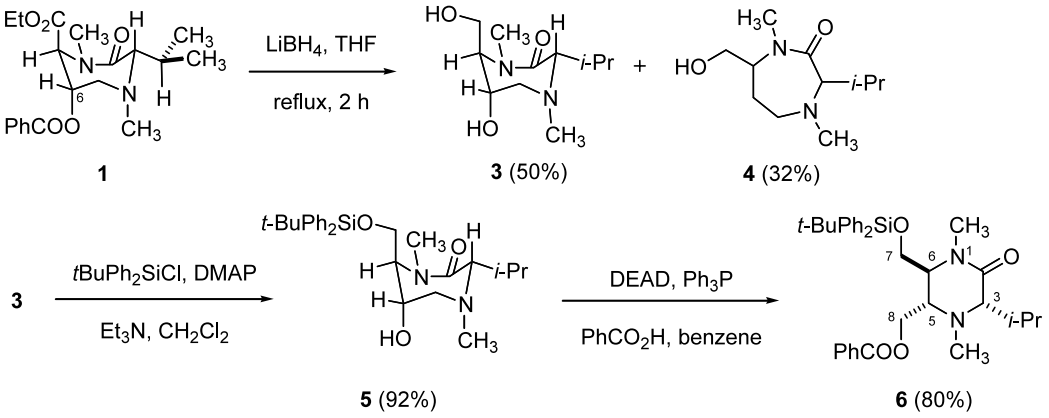


Scheme 1. Attempted Mitsunobu inversion at C-6.

decoupling). The stereochemical ambiguity was resolved by a NOESY experiment, the results of which are summarized in Figure 1. The several transannular (non-vicinal) NOE crosspeaks indicate that the six membered ring is in an unusual half-boat conformation, with pseudo-axial silyloxymethyl and benzoyloxymethyl substituents, and a pseudo-equatorial isopropyl. The pseudo-axial disposition of the silyloxymethyl group probably results from its avoidance of a steric interaction with the amide *N*-methyl.[7,8] Analogous conformational preferences, including the positions of the (pseudo-equatorial) isopropyl and (pseudo-axial) N-4-methyl substituents, were previously observed for the seven-membered diazepanone ring of **1** (compare Fig. 1 with the conformation of **1** in Scheme 1), as determined by NOESY studies and X-ray crystallography.[2] The relative stereochemical configuration at C-5 of **6** has been inverted (compared with C-6 of **5**) as a consequence of the Mitsunobu process.

The stereoselective ring contraction of **5** under Mitsunobu conditions likely results from participation of

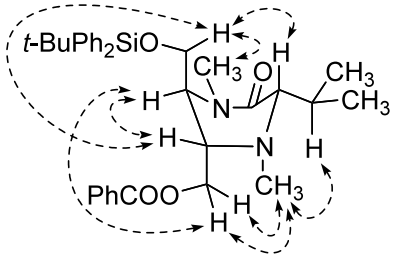
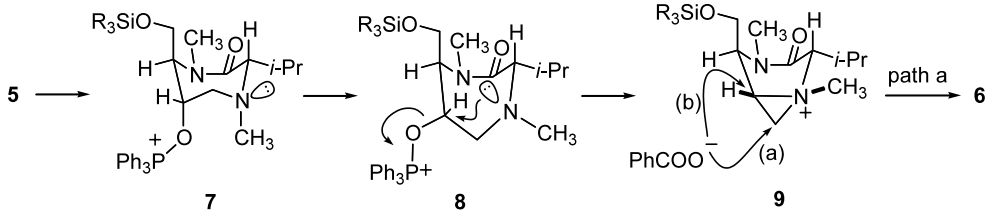


Figure 1. Selected NOESY crosspeaks for **6**.

the basic N-4 nitrogen with inversion at C-6 at the stage of the oxyphosphonium intermediate **7** (Scheme 2). The N-4 lone pair is initially well removed in space from the linear backside alignment with the C-6 carbon–oxygen bond as required for N-participation; therefore, a conformational change must occur to bring the lone pair closer to C-6. We suggest that the pseudo-chair **7** might ring-flip to the pseudo-boat conformation **8**, which features a pseudo-axial N-4 lone pair and a pseudo-equatorial leaving group, but retains the preferred disposition[2] of substituents at C-3 and C-7. The N-4 lone pair can then close with minimal distortion to the aziridinium ion **9**. The ion **9** might open by addition of benzoate at either the methylene carbon (path a), or at the more-substituted methine carbon (path b), but evidently follows path a exclusively. Examination of literature examples of aziridinium ring opening reactions with carboxylate nucleophiles[9–11] indicates that both types of ring opening (analogous to paths a and b) do occur, with the ratio dependent upon the reaction conditions. A Mitsunobu-generated aziridinium ion has been reported to give a mixture of displacement with retention and ring-expanded products with an added heterocyclic nitrogen nucleophile.[12,13] Ring opening of **9** by benzoate likewise would be expected to give a mixture, but the predominance of path a can be attributed in part to severe steric hindrance for path b beyond what is seen in the simpler literature examples. Additionally, the presence of nearby electron-withdrawing heteroatoms in **9** might reduce the polarizability of the CH–N^+ bond relative to the CH_2–N^+ bond.

Although it has a definite conformational preference, the diazepanone ring of **7** is apparently capable of flexing away from the pseudo-chair under the Mit-



Scheme 2. Proposed mechanism for ring contraction.

sunobu conditions to allow N-4 participation. The basic N-4 nitrogen in the diazepanone ring of liposidomycin precursors also interferes with glycosylation by participation at an anomeric center six atoms away.[14,15] The lesson from this and the Mitsunobu reaction is clear: the basic N-4 nitrogen of the diazepanone must be protected, perhaps as a non-nucleophilic amide, in order to carry out reactions that generate electrophilic carbon sites nearby.[16]

Acknowledgements

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16. Spectra for new compounds. Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$, δ, mult., integr., J in Hz, assignments by TOCSY) 4.24–4.18 (br m, H-6), 4.02 (dd, $J=6.0$, 11.2, H-8a), 3.95 (dd, $J=5.3$, 11.2, H-8b), 3.58–3.53 (br m, H-7), 3.16 (dd, $J=1.0$, 12.4, H-5a), 3.11 (s, N-1-C$\underline{H}_3$), 3.02 (d, $J=9.6$, H-3), 2.70 (dd, $J=7.7$, 12.4, H-5b), 2.33 (s, N-4-C$\underline{H}_3$) 2.24 (dsept, $J=9.6$, 6.5, C$\underline{H}$Me$_2$), 1.03 (d, $J=6.5$, CHC$\underline{H}_3$), 0.93 (d, $J=6.5$, CHC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 68.35, 62.03, 59.63, 38.67 (br), 35.70 (br), 25.44, 20.77, 19.45 (3 C's not observed); LC–FAB-MS m/z 253 (MNa^+) and 231 (MH^+). Compound **4**: ^{1}H NMR 4.08 (app br dt, $J=6.0$, 8.9, H-7), 3.92 (dd, $J=8.2$, 11.2, H-8a), 3.73 (dd, $J=5.6$, 11.2, H-8b), 3.27 (d, $J=9.9$, H-3), 3.22–3.13 (m, H-5ab), 3.00 (s, N-1-C$\underline{H}_3$), 2.23 (dsept, $J=10$, 6.6, C$\underline{H}$Me$_2$), 2.17 (s, N-4-C$\underline{H}_3$), 1.81–1.70 (m, H-6a), 1.30–1.20 (m, H-6b), 0.95 (d, $J=6.8$, CHC$\underline{H}_3$), 0.91 (d, $J=6.5$, CHC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 69.79, 63.96, 59.04, 34.84, 26.59, 22.68, 21.34, 19.62 (3 C's not observed); LC–FAB-MS m/z 215 (MH^+). Compound **5**: ^{1}H NMR 7.70–7.64 (m, four o-Ar-H's), 7.49–7.40 (m, six Ar-H's), 4.02 (br app t, $J=5.8$, H-6), 3.94 (dd, $J=6.8$, 10.6, H-8a), 3.85 (dd, $J=6.8$, 10.6, H-8b), 3.58 (br app q, $J=6.2$, H-7), 3.06 (s, N-1-C$\underline{H}_3$), 3.02 (dd, $J=2.0$, 12.6, H-5a), 2.62 (overlapping d, $J=9.1$, H-3), 2.66–2.58 (overlapping m, H-5b), 2.24 (s, N-4-C$\underline{H}_3$), 2.14 (dsept, $J=9.2$, 6.6, C$\underline{H}$Me$_2$), 1.09 (s, t-butyl), 0.92 (d, $J=6.6$, CHC$\underline{H}_3$), 0.77 (d, $J=6.6$, CHC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 135.79, 135.75, 132.77, 132.73, 130.36, 128.23, 69.96, 68.37 (br), 64.18, 59.67, 39.18 (br), 36.06 (br), 27.10, 26.63 (br), 20.93, 19.60, 19.36 (C=O not observed); LC–FAB-MS m/z 469 (MH^+). Compound **6**: ^{1}H NMR (assignments by COSY, NOESY, and HSQC) 8.01 (dd, $J=1.1$, 7.0, two o-Bz-H's), 7.65 and 7.63 (two overlapping dd's, $J=1.0$, 7.0, four o-Ph H's), 7.62 (tt, $J=1.3$, 7.0, p-Bz-H), 7.46 (app t, $J=7.0$, two m-Bz-H's), 7.43 (overlapping tt, $J=1.3$, 6.8, two p-Ph-H's) 7.38 (app t, $J=7.1$, two m-Ph-H's), 7.34 (app t, $J=7.1$, two m-Ph-H's), 4.35 (dd, $J=5.7$, 11.0, H-8a), 4.20 (dd, $J=8.4$, 11.0, H-8b), 3.74 (dq, $J=5.4$, 6.7, H-7ab), 3.52 (app ddd, $J=3.9$, 5.7, 8.5, H-5), 3.41 (app ddd, $J=3.8$, 5.3, 6.4, H-6), 2.95 (d, $J=4.8$, H-3), 2.86 (s, N-1-C$\underline{H}_3$), 2.57 (s, N-4-C$\underline{H}_3$), 2.26 (dsept, $J=4.8$, 6.9, C$\underline{H}$Me$_2$), 1.07 (s, t-butyl), 1.05 (d, $J=6.9$, CHC$\underline{H}_3$), 1.00 (d, $J=6.9$, CHC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 183.44, 170.05, 135.78, 135.73, 133.39, 130.25, 129.84, 128.70, 128.11, 68.55, 65.17, 62.99, 57.60, 34.46, 30.26, 27.03, 20.23, 19.59, 19.38; LC–FAB-MS m/z 573 (MH^+).