112.7, 111.7, 47.6, 47.1; MS *m/z* (rel intensity) 492 (2.2), 491 (4.4), 490 (12), 489 (6.7), 488 (M^+, 20), 384 (16), 382 (28), 348 (41), 255 (26), 245 (88), 243 (82), 209 (49), 140 (45), 118 (25), 106 (100); HRMS calcd for $C_{28}H_{26}N_4Cl_2$ (M^+) 488.1535, found 488.1533.

5,6,11,12,17,18,23,24-Octahydrotetrabenzo[*b*,*f*,*j*,*n*][1,4,8,13]tetraazacyclohexadecine (11). This compound was obtained by the reaction under reflux for 15 h, followed by the workup and chromatography (CH_2Cl_2/hexane, 1:2), as faintly yellowish crystals (53%): mp 236–239 °C; IR (KBr) 3343, 1603, 745 cm^{-1}; ^1H NMR δ 7.41–7.18 (m, 8 H), 6.91–6.73 (m, 8 H), 4.45 (br s, 2 H, 2 × NH), 4.30 (s, 4 H), 4.14 (s, 4 H), 3.50 (br s, 2 H, 2 × NH); ^{13}C NMR δ 147.9 (s), 137.4 (s), 137.3 (s), 132.0 (d), 131.0 (d), 129.9 (d), 129.0 (d), 123.0 (s), 119.9 (d), 118.2 (d), 111.7 (d), 111.4 (d), 47.7 (t), 45.8 (t); MS *m/z* (rel intensity) 421 (4.6), 420 (M^+, 10), 316 (9.3), 208 (21), 206 (31), 106 (43), 57 (64), 55 (61), 43 (100), 41 (92). Anal. Calcd for $C_{28}H_{28}N_4$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.11; H, 6.85; N, 13.43.

Reduction of 4a with Sodium Cyanoborohydride. 11,12,23,24-Tetrahydrodibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*][1,5]diazocine-6,18(5*H*,17*H*)-dione (6). To a stirred mixture of **4a** (120 mg, 0.272 mmol) in glacial acetic acid (10 mL) was added $NaBH_3CN$ (170 mg, 2.71 mmol) under nitrogen. After stirring for 2 h at rt and for 8 h at 60 °C, the mixture was poured into ice–water, basified with 50% aq NaOH, and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with saturated aq NaCl solution and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave crude product, which was chromatographed on a silica gel column (CH_2Cl_2/AcOEt, 1:10) to afford the tetrahydro derivative **6** as colorless crystals (109 mg, 90%): mp >300 °C; IR (KBr) 3306, 1634, 1613, 752 cm^{-1}; ^1H NMR δ 7.91 (ddd, 2 H, *J* = 7.8, 1.4, 0.4 Hz), 7.42–7.11 (m, 10 H), 6.83 (dt, 2 H, J = 1.2, 8.0 Hz), 6.64–6.59 (m, 2 H), 6.11 (s, 2 H), 4.65 (br s, 2 H, 2 × NH); ^{13}C NMR δ 164.6, 146.8, 139.0, 135.2, 134.0, 132.1, 131.8, 130.9, 129.3, 129.2, 120.2, 117.8, 116.4, 75.4; MS *m/z* (rel intensity) 445 (33), 444 (M^+, 100), 443 (27), 442 (29), 441 (30), 325 (26), 324 (78), 297 (27), 120 (26); HRMS calcd for $C_{28}H_{20}N_4O_2$ (M^+) 444.1584, found 444.1586.

The reduction of **6** with BH_3·THF complex under the same conditions as above, followed by workup and chromatography, afforded **51** (39%).[15]

(15) We are grateful for financial support by the Ministry of Education, Japanese Government (Grant-in-Aid 02555174).

First Asymmetric Synthesis of the Tröger's Base Unit on a Chiral Template

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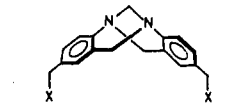
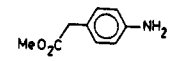
There has recently been a great deal of interest in using the V-shaped Tröger's base unit in the construction of molecular receptors.[1] Asymmetric synthesis of Tröger's base[2] **1** or its analogues has been a challenge since the enantiomers racemize under acidic reaction conditions.[3,4] We now report the *first asymmetric synthesis*[5] of the Tröger's base unit in ca. 40% ee using 7-deoxycholic acid as a chiral template.

In connection with our long-term program on the design, synthesis, and evaluation of novel molecular receptors using readily available natural products as templates it occurred to us that 7-deoxycholic acid, with two "parallel" hydroxyl groups at the 3 and 12 positions, could serve as a novel template to couple two covalently bound fragments, *provided that geometric requirements for the coupling are met*. Removal of the steroid would then constitute a template construction of a bimolecular reaction product.[6]

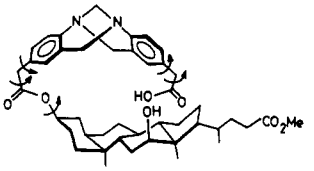
Since the steroid is chiral, one could expect some diastereoselection in the coupling process if the coupling creates a stereogenic center(s). We decided to attempt the synthesis of a Tröger's base analogue since the coupling of two aniline units creates two stereogenic nitrogen atoms and produces a rigid V-shaped unit. Computer modeling using the DTMM (Desk Top Molecular Modeller) program[7–11] suggested that compound **2** would be able to form a bis-lactone on the steroid surface using the two hydroxyl groups. This implied that **4** would be a logical precursor for the cyclization.



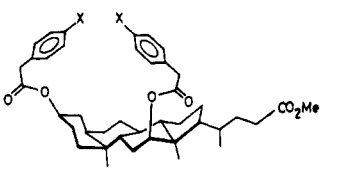
1 : X = H
2 : X = COOH
7 : X = COOMe



6



3



4 : X = NO_2
5 : X = NH_2

Compound **4** was easily synthesized in 83% yield from methyl 7-deoxycholate[12] and (*p*-nitrophenyl)acetyl chloride using a modified Oppenauer procedure.[13] Reduction with

† This paper is dedicated to the memory of my father and to Professor Ronald Breslow on the occasion of his 61st birthday.

(1) Wilcox, C. S. *Tetrahedron Lett.* **1985**, *26*, 5749. Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865. Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. *J. Org. Chem.*, **1988**, *53*, 98. Webb, T. H.; Wilcox, C. S. *J. Org. Chem.* **1990**, *55*, 363.

(2) Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225. Prelog, V.; Wieland, P. *Helv. Chim. Acta.* **1944**, *27*, 1127.

(3) Mason, S. F. *Molecular Optical Activity & the Chiral Discriminations*; Cambridge University Press: Cambridge, 1982; p 50. Greenberg, A.; Molinaro, N.; Lang, M. *J. Org. Chem.* **1984**, *49*, 1127.

(4) A new resolution procedure (via a second-order asymmetric transformation) has been reported: Wilen, S. H.; Qi, J. Z.; Williard, P. G. *J. Org. Chem.* **1991**, *56*, 485.

(5) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554. These authors reported an elegant synthesis to form a Tröger's base analogue via diastereoselective cyclization of a chiral precursor. The Tröger's base unit, however, was not cleaved from the cyclized product.

(6) For recent examples of selective template coupling see: Miyano, S.; Fukushima, H.; Honda, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249. Ueno, A.; Moriwaki, F.; Iwama, Y.; Suzuki, I.; Osa, T.; Ohta, R.; Nozoe, S. *J. Am. Chem. Soc.* **1991**, *113*, 7034.

(7) We thank the Bioinformatic Center, Indian Institute of Science, for providing the computational facilities.

(8) The DTMM (Desk Top Molecular Modeller) program was used to generate compound **3** (both diastereomers) using the X-ray coordinates of deoxycholic acid[9] and **1**.[10] Rotations about the indicated (see arrows in **3**) single bonds (keeping both the ester and the carboxylic acid in the s-trans configuration) revealed that through *these rotations* the COOH group in compound **3** can be made to come very close (<0.5 Å) to the 12-OH group. This suggested the feasibility of the template synthesis as we felt that minor bond/dihedral angle adjustments would make a good fit of the two functionalities.

(9) Popovitz-Biro, R.; Tang, C. P.; Chang, H. C.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 4043.

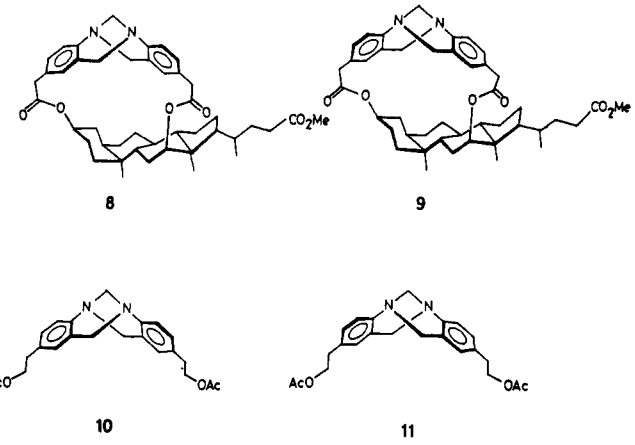
(10) Larson, S. B.; Wilcox, C. S. *Acta Crystallogr., Sect. C* **1986**, *42*, 224.

(11) For a program ("CAVEAT") to facilitate the structure-derived design of biologically active molecules, see: Bartlett, P. A.; Shea, G. T.; Telfer, S. J.; Waterman, S. In *Molecular Recognition: Chemical and Biochemical Problems*; Roberts, S. M., Ed.; Special publication no. 78; Royal Society of Chemistry: London, 1989; p 182.

(12) Fieser, L.; Rajagopalan, S. *J. Am. Chem. Soc.* **1949**, *71*, 3935.

0022-3263/92/1957-6979$03.00/0

$SnCl_2 \cdot 2H_2O$ in ethanol[14] at 70 °C provided diamine **5** which was used directly for the cyclization. The reaction conditions for effecting Tröger's base formation[1,2] require alcoholic solvents in the presence of aqueous HCl. We anticipated solubility problems with **5** in such a medium. A more serious problem was the possible hydrolysis/ester exchange under strongly acidic conditions. Indeed, attempted Tröger's base analogue formation from model compound **6** in CD_3OD/35% formalin/aqueous HCl and analysis of diester **7** (10% yield) by ^1H NMR and mass spectrum revealed over 90% ester exchange.[15] *This problem was solved by carrying out the cyclization of 5 (0.012 M) in dry methylal in the presence of methanesulfonic acid (0.13 M) for 2 days.*[16] Diastereomeric mixtures of **8** and **9** were obtained in a 2.5:1 ratio (12-H of steroid at δ 5.08 and 4.95 for major and minor isomers, respectively) in 25–35% isolated yield. This mixture was reduced (LAH, THF, reflux, 23 h) to remove the chiral template, and the diol was acetylated (Ac_2O, pyr). Careful purification (PTLC) afforded **10** plus **11** which was identical to the racemic product derived from **7** by reduction and acetylation (TLC, IR, NMR, MS). This mixture (**10** + **11**) had $[\alpha]^{25}_D = +83°$ (*c* 0.84, $CHCl_3$) and showed a CD spectrum in 1% $CHCl_3/CH_3OH$ with a negative peak at 286 nm ($\Delta\epsilon_{286} = -2.12$ M^{-1} cm^{-1}). The absolute configuration of the (+)-enantiomer of **1**, with a negative CD peak at 292 nm, was reported to be *R,R* from its CD spectrum analysis.[17] However, the configuration has recently been revised to *S,S* from the X-ray analysis of a salt.[4] The remote substituent (CH_2OAc) in **10**/**11** is unlikely to perturb the chromophore, and thus we assign the absolute configuration (at N) of our major product to be *S,S* (**8** and **10**).



8 **9** **10** **11**

It was not possible to separate the diastereomeric mixture of **8** and **9** by chromatography (including C18 HPLC). However, slow crystallization of the mixture from ethanol afforded the pure *minor* diastereomer **9**[18] which was fully characterized.[19] LAH reduction and acetylation of this compound afforded Tröger's base analogue **11** with $[\alpha]^{25}_D = -195°$ (*c* 0.51, $CHCl_3$), $\Delta\epsilon_{286} = +5.62$ M^{-1} cm^{-1} (0.4% $CHCl_3$/MeOH).[20,21]

We have thus been able to execute a novel asymmetric synthesis of the methanodibenzodiazocine unit of Tröger's base on a chiral steroid template. Further work to improve the diastereoselectivity through structural modification in **4** is in progress. We believe that our template synthesis strategy would prove useful in the construction of other complex molecules through a similar bimolecular coupling approach. We are currently investigating some other coupling processes, and these results will be reported in due course.

Experimental Section

Methyl 3α,12α-Bis(((4-nitrophenyl)acetyl)oxy)cholanate (4). A mixture of (*p*-nitrophenyl)acetyl chloride (1.44 g, 7.21 mmol), calcium hydride (0.92 g, 21.8 mmol), benzyltriethylammonium chloride (0.058 g, 0.21 mmol), and methyl deoxycholate (1.12 g, 2.75 mmol) in dry toluene (7 mL) was heated to 65–70 °C (oil bath) for 7 h with magnetic stirring. After cooling, the mixture was filtered and the residue was washed with chloroform. The combined organic layer was washed with 7% $NaHCO_3$ solution and 30% NaCl solution and finally dried over anhyd Na_2SO_4. Volatiles were removed in vacuo, and the crude product was purified by column chromatography on silica gel using chloroform and 2% ethyl acetate/chloroform as eluents. The pure product was isolated in 83% yield (1.68 g). Crystallization from a mixture of dichloromethane and ethanol gave colorless needles of **4** (mp 137–138 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 8.24 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 4 H), 5.11 (s, 3 H), 4.72 (br s, $w_{1/2}$ = 26 Hz, 1 H), 3.81 (s, 2 H), 3.76 (s, 2 H), 3.67 (s, 3 H), 2.35–2.0 (m, 2 H), 2.0–0.93 (br m), 0.88 (s, 3 H), 0.71 (d, J = 5.8 Hz, 3 H), 0.70 (s, 3 H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 174.19, 169.64, 168.67, 147.00, 141.58, 130.20, 123.49, 76.79, 75.16, 51.32, 49.05, 47.32, 44.93, 41.68, 40.92, 35.40, 34.31, 33.88, 32.04, 30.52, 27.16, 26.51, 25.86, 25.32, 23.26, 22.83, 17.30, 12.10. IR (Nujol): 2920 (s), 2854 (s), 1731 (s), 1608 (m), 1518 (m), 1464 (s), 1380 (m), 1263 (m) cm^{-1}. $[\alpha]^{25}_D = +64.5°$ (*c*, 4.06, $CHCl_3$). Anal. Calcd for $C_{41}H_{52}N_2O_{10}$: C, 67.19; H, 7.15; N, 3.82. Found: C, 67.55; H, 7.18; N, 3.52.

Tröger's Base Analogues 8/9. A mixture of compound **4** (1.437 g, 1.96 mmol), $SnCl_2 \cdot 2H_2O$ (3.319 g, 14.7 mmol) and ethanol (15 mL) was stirred magnetically under a nitrogen atmosphere at 68–71 °C for 3 h. The reaction mixture was partitioned between ethyl acetate (70 mL) and cold 7% $NaHCO_3$ solution (75 mL), stirred with Celite for 20 min, and then filtered. The residue was washed with a total of 25 mL of ethyl acetate and 20 mL of water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The pooled organic layer was washed with 7% $NaHCO_3$ solution and 30% NaCl solution and dried over anhyd Na_2SO_4, and volatiles were removed in vacuo. The crude diamine **5** (1.329 g) was dissolved in dry methylal (155 mL), methanesulfonic acid (1.95 g, 20.29 mmol) was added, and the mixture was refluxed for 2 days under a nitrogen atmosphere with magnetic stirring. After cooling, the reaction mixture was diluted with 20 mL of ethyl acetate and water (10 mL) and ammonia (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted with 10 mL of ethyl acetate. The combined organic layer was washed with 7% $NaHCO_3$ solution and 30% NaCl solution and dried over anhyd Na_2SO_4. Volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using 25% ethyl acetate/chloroform as the eluant. The product obtained in 37% yield (0.52 g) was further purified by a Chromatotron using the same solvent mixture. The overall yield of the pure product (pale yellow solid) was 25% (0.35 g). ^1H NMR

(13) Oppenauer, R. V. *Monatsch.* **1966**, *97*, 62. $PhCH_2N^+Et_3Cl^-$ was used instead of n-Bu_4N^+ I^-.

(14) Bellamy, F. D.; 'Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.

(15) Mass spectral measurement showed a 1:18:81 ratio of d_0:d_3:d_6 in the molecular ion. ^1H-NMR revealed only ca. 10% of the expected intensity of the CH_3O signal.

(16) We find that under these conditions Tröger's base analogue **7** is obtained from **6** in 31% (unoptimized) yield.

(17) Mason, S. F.; Vane, G. W.; Schofield, K.; Wells, R. J.; Whitehurst, J. S. *J. Chem. Soc. B* **1967**, 553.

(18) We have not yet been able to grow crystals of **9** suitable for X-ray analysis.

(19) ^1H NMR, ^{13}C NMR, HRMS, UV, CD, $[\alpha]_D$, elemental analysis, mp.

(20) We have observed that a ca. 11:1 ratio of **8**/**9** (obtained after crystallization of the minor diastereomer) remained essentially unaltered (NMR) when subjected to reaction conditions (0.007 M in dry methylal, 0.092 M CH_3SO_3H, reflux) for 24 h. Under identical conditions the 2.5:1 ratio of **10**/**11** racemized completely. This implies that the product ratio is *not* thermodynamically controlled.

(21) The % ee of **10**/**11** (obtained from the 2.5/1 mixture of **8**/**9**) calculated from $[\alpha]^{25}_D$ and CD data are 43 and 38, respectively.

(400 MHz, $CDCl_3$): δ (for major diastereomer 8 only) 7.34 (d, J = 8.1 Hz, 1 H), 7.07 (d, J = 8.1 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 6.94 (d, J = 7.9 Hz, 1 H), 6.69 (s, 1 H), 6.66 (s, 1 H), 5.08 (s, 1 H), 4.62 (d, J = 16.4 Hz, 1 H), 4.61 (d, J = 16.3 Hz, 1 H), 4.56 (br m, $w_{1/2}$ = 27 Hz, 1 H), 4.42 (s, 2 H), 4.17 (d, J = 16.5 Hz, 1 H), 4.01 (d, J = 16.4 Hz, 1 H), 3.66 (s, 3 H), 3.64 (d, J = 17.8 Hz, 1 H), 3.62 (d, J = 13.7 Hz, 1 H), 3.40 (d, J = 14.0 Hz, 1 H), 3.39 (d, J = 16.5 Hz, 1 H), 2.38–2.1 (m, 2 H), 1.9–0.85 (m), 0.85 (s, 3 H), 0.78 (d, J = 6.3 Hz, 3 H), 0.70 (s, 3 H), 0.46 (q, J = 11.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (for both diastereomers) 174.49, 174.43, 170.97, 170.83, 170.70, 146.36, 146.21, 146.17, 146.13, 129.84, 129.79, 128.65, 128.52, 128.49, 128.37, 127.95, 127.69, 127.58, 127.48, 127.08, 125.12, 124.56, 124.48, 124.30, 78.08, 76.38, 74.95, 74.53, 67.81, 67.46, 59.85, 59.68, 59.40, 59.29, 51.46, 48.71, 48.18, 48.01, 47.75, 45.53, 45.07, 42.31, 42.24, 42.09, 41.81, 41.56, 40.18, 35.96, 35.82, 34.92, 34.80, 34.68, 34.59, 34.56, 34.49, 34.43, 32.72, 32.57, 30.95, 30.78, 29.62, 27.59, 27.36, 27.21, 26.43, 26.37, 26.08, 25.74, 25.58, 25.51, 23.73, 23.49, 23.42, 17.57, 17.38, 12.39, 12.12. IR (neat, thin film on NaCl plate): 2944 (m), 1728 (s), 1497 (m), 1437 (w), 1260 (s) cm^{-1}. UV log ε (284 nm) = 3.24 (c 1.58 × 10^{-4} M, 2% $CHCl_3/CH_3OH$).

Tröger's Base Analogue 9. The mixture of diastereomers (8/9, 0.350 g) was dissolved in warm ethanol (20 mL) with the aid of a few drops of dichloromethane. The solution was left at room temperature (ca. 26 °C) for a few days after seeding with a crystal of 9. The colorless needles were collected, washed with cold ethanol, and dried to give 0.045 g of pure 9. Mp: 242–244 °C dec. R_f: 0.2, 25% ethyl acetate/chloroform. ^1H NMR (200 MHz, $CDCl_3$); δ 7.27 (dd, J = 8.3, 1.6 Hz, 1 H), 7.13 (d, J = 8.3 Hz, 1 H), 7.02 (d, J = 8.2 Hz, 1 H), 6.94 (dd, J = 8.2, 1.8 Hz, 1 H), 6.86 (s, 1 H), 6.73 (s, 1 H), 4.95 (s, 1 H), 4.66 (d, J = 16.4 Hz, 1 H), 4.62 (d, J = 16.5 Hz, 1 H), 4.55 (br m, $w_{1/2}$ = 30 Hz, 1 H), 4.39 (s, 2 H), 4.15 (d, J = 16.5 Hz, 1 H), 4.10 (d, J = 16.5 Hz, 1 H), 3.66 (s, 3 H), 3.59 (d, J = 14.2 Hz, 1 H), 3.47 (s, 2 H), 3.43 (d, J = 12.7 Hz, 1 H), 2.38–1.0 (br), 0.87 (s, 3 H), 0.81 (d, J = 5.9 Hz, 3 H), 0.71 (s, 3 H), 0.38 (q, J = 11.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.45, 170.97, 170.85, 146.45, 146.31, 129.89, 128.69, 128.62, 128.53, 127.72, 127.55, 127.16, 127.08, 124.61, 124.51, 78.12, 74.57, 67.54, 59.46, 59.35, 51.48, 48.23, 48.07, 45.59, 42.30, 42.15, 41.86, 36.03, 34.85, 34.74, 34.54, 32.79, 30.99, 30.98, 27.65, 27.44, 26.48, 26.42, 25.63, 23.78, 23.54, 17.43, 12.16. FTIR: 2939 (s), 2864 (m), 1722 (s), 1494 (s), 1444 (m), 1331 (w), 1260 (s), 1223 (m), 1205 (m), 1150 (s), 1114 (w), 1097 (w), 1066 (w), 1012 (m). Deconvolution (with 4 cm^{-1} resolution) showed the following carbonyl peaks: 1736, 1724, 1714 cm^{-1}. UV: log ε (283 nm) = 3.23 (c 1.27 × 10^{-4} M, 0.1% $CHCl_3/CH_3OH$). LRMS: 293 (22), 338 (17), 371 (12), 708 (100). HRMS: exact mass calcd for $C_{44}H_{56}N_2O_6$ 708.4139, found 708.4154. $[\alpha]^{25}_D$ = +144.3° (c 0.07, ethanol). CD: $\Delta\epsilon_{286}$ = +1.67 M^{-1} cm^{-1} (c 1.27 × 10^{-4} M, 0.1% $CHCl_3/CH_3OH$). Anal. Calcd for $C_{44}H_{56}N_2O_6$: C, 74.54; H, 7.96; N, 3.95. Found: C, 74.38; H, 8.12; N, 3.58.

2,8-Bis(2-acetoxyethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (10/11). A mixture of diastereomers 8 and 9 (0.074 g, 0.104 mmol) was refluxed with a solution of LAH (0.034 g, 0.896 mmol) in THF (6.8 mL, freshly distilled from LAH) for 23 h. The reaction mixture was cooled, and finely powdered $MgSO_4 \cdot 7H_2O$ was added to quench the excess of LAH. The mixture was stirred, diluted with ethyl acetate (10 mL), and filtered through a bed of Celite. The solvent was removed, and the crude product (0.065 g) was stirred with acetic anhydride (1.08 g, 10.6 mmol) and pyridine (0.99 g, 12.5 mmol) at 27–30 °C under a nitrogen atmosphere for 16 h. Volatiles were removed under high vacuum, and the crude product was first purified by flash chromatography on silica gel using 25% ethyl acetate/chloroform as the eluant. The partially purified product (0.023 g, 62%) was further purified by PTLC (silica gel GF_{254}) using 25% ethyl acetate/chloroform as the developing agent. The product was isolated in 46% yield (0.017 g). ^1H NMR (90 MHz, $CDCl_3$): δ 7.03 (s, 4 H), 6.75 (s, 2 H), 4.68 (d, J = 16.6 Hz, 2 H), 4.28 (s, 2 H), 4.20 (t, J = 7.6 Hz, 4 H), 4.11 (d, J = 16.6 Hz, 2 H), 2.81 (t, J = 7.1 Hz, 4 H), 2.02 (s, 6 H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 170.61, 146.34, 133.12, 127.60, 126.95, 124.89, 66.60, 64.54, 58.36, 34.31, 20.66. IR (neat): 2944 (m), 1737 (s), 1668 (m), 1617 (w), 1497 (s), 1440 (m), 1389 (m), 1368 (s), 1332 (m), 1251 (s), 1209 (s), 1164 (w), 1143 (w), 1116 (m), 1098 (m), 1065 (s), 1035 (s) cm^{-1}. UV: log ε (282.5 nm) = 3.23 (c 9.79 × 10^{-5} M, 1.2% $CHCl_3/CH_3OH$). $[\alpha]^{25}_D$ = +83.2° (c 0.84, $CHCl_3$). CD: $\Delta\epsilon_{286}$ = −2.12 M^{-1} cm^{-1} (c 2.12 × 10^{-4} M, 1% $CHCl_3/CH_3OH$). LRMS: 43 (48), 274 (77), 334 (40), 394 (100). HRMS: exact mass calcd for $C_{23}H_{26}N_2O_4$ 394.1893, found 394.1862.

Spectral Data on Authentic 10/11 (Racemic). ^1H NMR (90 MHz, $CDCl_3$): δ 7.04 (s, 4 H), 6.75 (s, 2 H), 4.67 (d, J = 16.6 Hz, 2 H), 4.27 (s, 2 H), 4.18 (t, J = 7.2 Hz, 4 H), 4.10 (d, J = 15.4 Hz, 2 H), 2.79 (t, J = 7.2 Hz, 4 H), 2.00 (s, 6 H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 170.61, 146.34, 133.12, 127.60, 126.95, 124.89, 66.60, 64.54, 58.36, 34.31, 20.66. IR (neat): 2944 (m), 1740 (s), 1665 (w), 1617 (w), 1497 (s), 1440 (m), 1389 (m), 1365 (m), 1332 (m), 1242 (s), 1209 (s), 1164 (w), 1143 (w), 1113 (m) cm^{-1}. UV: log ε (283 nm) = 3.24 (c 2.16 × 10^{-4} M, 2% $CHCl_3/CH_3OH$). LRMS: 43 (35), 274 (74), 334 (40), 394 (100). HRMS: exact mass calcd for $C_{23}H_{26}N_2O_4$ 394.1893, found 394.1880.

Spectral Data on Pure Enantiomer 11. ^1H NMR (90 MHz, $CDCl_3$): δ 7.03 (s, 4 H), 6.75 (s, 2 H), 4.67 (d, J = 16.6 Hz, 2 H), 4.27 (s, 2 H), 4.20 (t, J = 7.3 Hz, 4 H), 4.12 (d, J = 16.6 Hz, 2 H), 2.81 (t, J = 7.3 Hz, 4 H), 2.03 (s, 6 H). $[\alpha]^{25}_D$ = −195° (c 0.51, $CHCl_3$). CD: $\Delta\epsilon_{286}$ = +5.62 M^{-1} cm^{-1} at 298 K (c 5.12 × 10^{-5} M, 0.4% $CHCl_3/CH_3OH$). UV: log ε (283 nm) = 3.25 (c 5.12 × 10^{-5} M, 0.4% $CHCl_3/CH_3OH$).

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Six-Membered Cyclic β-Keto Esters by Tandem Conjugate Addition–Dieckmann Condensation Reactions

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Carbon functionalization of anions generated by conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds has found wide use in organic synthesis.[2-4] One subset of these reactions, cycloacylations, has provided an efficient synthetic route to highly functionalized cyclic compounds. Most notable among these is an account detailing the formation of dimethyl cyclohexanone-2,4-dicarboxylates by addition of lithium dialkylcuprates to methyl crotonate[5] and three reports describing conjugate addition–cycloacylations to form substituted cyclopentenones[6] and cycloalkanones.[7,8] One of these reports[7] has described the preparation of C-5-substituted 2-oxocyclopentanecarboxylate esters by cuprate addition to dimethyl (*E*)-2-hexenedioate and applied this technology to the synthesis (±)-mitsugashiwalactone. Since we required access to 2-oxocyclohexanecarboxylate esters bearing substitution at C-6, we were interested in the possibility of adapting this conjugate addition–Di-

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