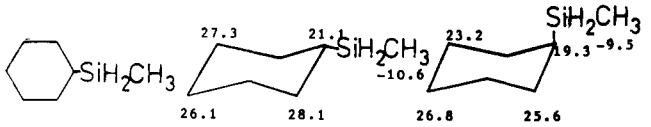
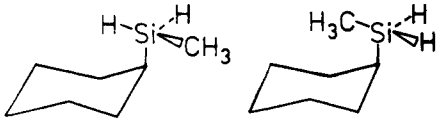
reflect the conformational proportions.) The significant upfield γ-effect of SiH_3 (−3.8 ppm, based on cyclohexane, δ_C = 27.0 ppm) is noteworthy and should be compared with −6.4 ppm for (axial) methyl in methylcyclohexane.[4] However, the patterns of ring carbon shifts for **3** and **2** resemble those for axial and equatorial methylcyclohexane, i.e., in both axial conformers all ring carbons except C_4 are to higher field than the corresponding signals in the equatorial conformers. These trends can be rationalized in terms of the γ-gauche effect, and anti-vicinal hydrogen–hydrogen interactions.[4]

Cyclohexylmethylsilane (**4**) was also examined, but the 400-MHz ^1H spectrum (188 K) did not provide a useful measure of the conformational ratio, although broad minor signals at δ 3.47 (SiH_2, axial) and δ 0.08 (SiH_2CH_3) were discernible. (The corresponding signals for the equatorial



(4) (5) (6)

conformer were δ 3.43 and 0.02, respectively.) Examination of the dideuterio derivative (SiD_2CH_3) did not afford improved resolution. Fortunately, the 100-MHz ^{13}C spectrum at 188 K was more revealing, and a set of minor broadened signals, with appropriate relative intensities, could be ascribed to the minor form and are assigned in **5** and **6**. Two measures of conformational populations were possible. Integration of the axial CH_3 signal (−9.5 ppm) against the lower field ^{29}Si satellite of the (major) equatorial CH_3 signal ($^1J_{^{29}SiCH_3}$ = 50 Hz) provided $-\Delta G°_{188} = 1.6 \pm 0.05$ kcal/mol, whereas similar treatment of the C1 signal (19.3 ppm in **6**) and the lower field satellite about C1 (21.1 ppm in **5** ($J_{^{29}Si-C}$ = 56 Hz)) led to $-\Delta G°_{188}$ = 1.65 kcal mol. The almost identical γ-gauche effects of axial SiH_3 and SiH_2CH_3 (in **3** and **6**) are expected on the basis that the asymmetric conformation of **6** (i.e., **7**) is more favoured than arrangement **8**, on both enthalpic and statistical grounds.[1]



(7) (8)

Certain calculated *A* values for SIH_3 and SiH_2CH_3 agree well with those reported here. For example, Ouellette[1] reported values of 1.26 and 1.62 kcal/mol on the basis of an early empirical force field, whereas Cartledge[2] arrived at 1.1–1.2 kcal/mol for SiH_3 on the basis of an MM2-82 parameter set and certain new torsion terms. That SiH_3 has a smaller *A* value than CH_3 (1.74 kcal/mol) can be understood in terms of lower nonbonded terms (E_{nb}) between the "over-the-ring" hydrogen and the C3,5 methylenes (in **3**) compared with axial methylcyclohexane, because of longer C–Si and Si–H bonds. Bending force constants involving silicon are lower than for carbon, and angle deformations about Si could lead to "opening-up" of the H–Si–C angle and a "closing-in" of the Si–C_1–H_1 angle, both of which would reduce E_{nb}.[5] $A_{Si(CH_3)_3}$ of 2.5 kcal/mol has been reported previously.[6]

(4) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 225.
(5) Ouellette, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 7674.
(6) Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153.

Experimental Section

Compounds. Commercially available (Petrarch Systems) cyclohexyltrichlorosilane was slowly added, as an ether solution, to a well-stirred ether suspension of lithium aluminum hydride (2 mol equiv) at 0 °C. After addition was complete, the reaction was stirred at room temperature for about 30 min and then flash distilled, with all volatiles being condensed at −78 °C. Ether was carefully removed, and the residual oil was distilled (Kugelrohr apparatus) and then redistilled. Cyclohexylsilane thus obtained showed no impurities by capillary gas chromatography nor by the subsequent ^1H and ^{13}C NMR examinations, the details of which are discussed in the text.

An identical procedure was employed to convert cyclohexylmethyldichlorosilane to cyclohexylmethylsilane.

Cyclohexylsilane was purified by Kugelrohr distillation (oven temperature 55 °C/20 mmHg) (lit.[7] 119.5 °C/739.5 mmHg); accurate mass = 114.0860 (calcd for $C_6H_{14}{}^{28}Si$ = 114.0864).

Cyclohexylmethylsilane was also purified by Kugelrohr distillation (oven temperature 58 °C/20 mmHg); accurate mass = 128.1025 (calcd for $C_7H_{16}{}^{28}Si$ = 128.1021).

NMR spectra were obtained with a JEOL-GX-400 spectrometer using the 5-mm dual ^1H, ^{13}C probe. ^{13}C spectra were acquired by using 64K data points and bilevel decoupling, with a 3-s recycle time, 30° pulse, and 20-kHz spectral width. ^1H spectra were acquired by using 32K data points, a 5-s recycle time, 30° pulse, and 4-kHz spectral width. The temperature control unit for the probe was calibrated with reference to the temperature calibration curves[8] for a methanol sensor at low temperature (a Varian sealed tube sample of methanol). Temperatures are considered accurate to ±1.5 °C.

Acknowledgment. K.G.P. and W.K. are grateful to the Australian Research Council for partial support of this work, and informative exchanges with Prof. Frank Cartledge (Louisiana State University) are acknowledged.

Registry No. 1, 18162-96-4; 4, 2096-99-3; cyclohexyltrichlorosilane, 98-12-4; cyclohexylmethyldichlorosilane, 5578-42-7.

(7) Opitz, H. E.; Peake, J. S.; Nebergall, W. H. *J. Am. Chem. Soc.* **1956**, *78*, 292.
(8) *Practical NMR Spectroscopy*; Martin, M. L.; Martin, G. J.; Delpuech, J. J., Eds.; Heyden and Son: Philadelphia 1980; Appendix A6.3, p 445.

Synthesis of Saframycins. 3. Preparation of a Key Tricyclic Lactam Intermediate to Saframycin A

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In the conduct of synthetic efforts on the antitumor antibiotics saframycins (**1–3**, Chart I), safracins (**4**, **5**), and saframycins Mx (**6**, **7**), we recentry reported a total synthesis of (±)-**2** from the tricyclic lactam **11**.[1] To extend the scope of the synthetic route of the saframycins, we have focused our attention on the synthetic studies of **1**.[3]

(1) (a) Kubo, A.; Saito, N.; Nakamura, M.; Ogata, K.; Sakai, S. *Heterocycles* **1987**, *26*, 1765–1770. (b) Kubo, A.; Saito, N.; Yamauchi, R.; Sakai, S. *Chem. Pharm. Bull.* **1987**, *35*, 2158–2161. (c) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295–4310. For an alternative total synthesis of (±)-**2** see ref 2.
(2) Fukuyama, T.; Sachleben, R. *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958.

0022-3263/89/1954-5391$01.50/0

Scheme I

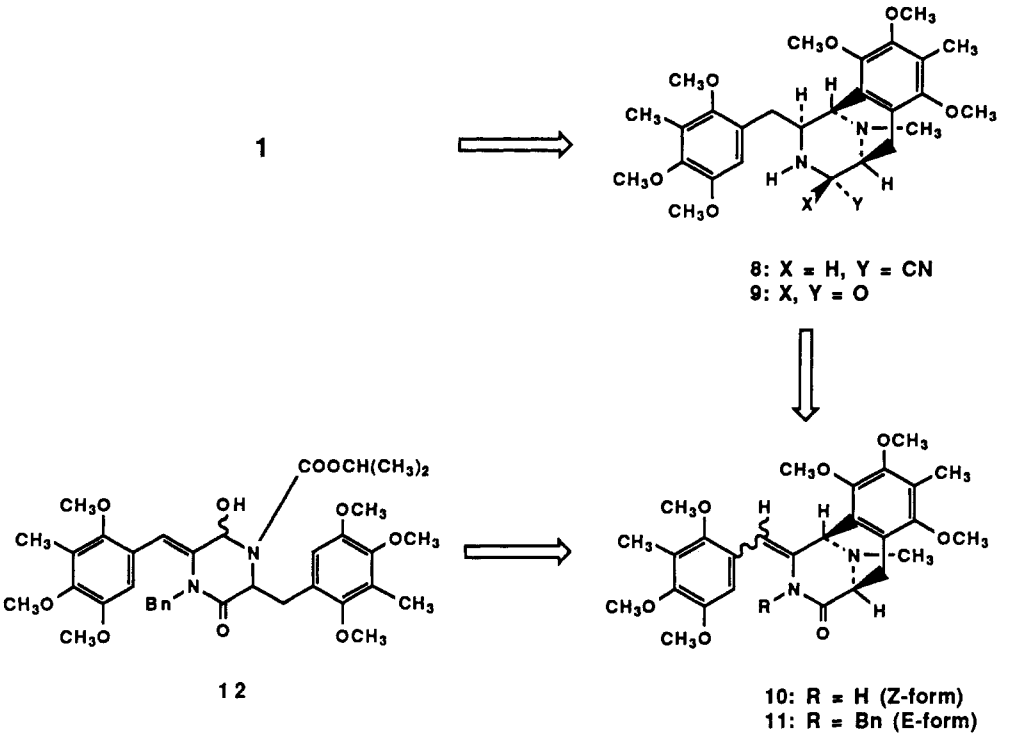
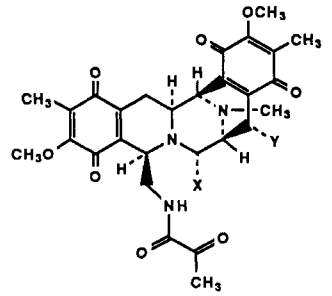
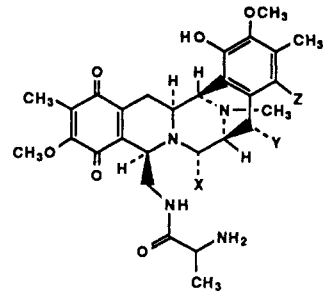


Chart I



1: X = CN, Y = H
2: X = Y = H
3: X = H, Y = OCH_3



4: X = Y = Z = H
5: X = OH, Y = Z = H
6: X = Z = OH, Y = OCH_3
7: X = H, Y = OCH_3, Z = OH

Our initial strategy for the synthesis of **10** was based on the retrosynthetic analysis outlined in Scheme I. We envisioned formation of **10** via debenzylation of the lactam **11**, which was prepared from the allylic alcohol **12** in three steps. Since all attempts to remove the *N*-benzyl group of **11** failed, we sought the synthesis of **10** by using *p*-methoxybenzyl group as amide protecting group.[4] In this paper, we report some progress toward this goal and the synthesis of **10** in seven steps in an overall yield of 31%.

Results and Discussion

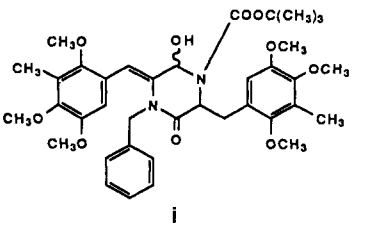
Substrate **16** was prepared from the 1-acetyl-2,5-piperazinedione **13**[5] in three steps by the methods recently disclosed[1] in our total synthesis of saframycin B (**2**). Reduction of **16** with lithium tri-*tert*-butoxyaluminum hydride afforded the allylic alcohol **17** (contaminated with a small amount of **15**), which on treatment with formic acid afforded **19** in 42% overall yield. On the other hand, we examined the dehydration and cyclization of the allylic alcohol **17** under nonacidic conditions (Scheme II). Methanesulfonyl chloride and triethylamine in dichloromethane under reflux brought about mild and efficient dehydration/cyclization of allylic alcohol **17** to afford the corresponding (*E*)-1,5-imino-3-benzazocine **19** in 70% yield.[6] The *E* stereochemical assignment to **19** was confirmed by spectral data (see Experimental Section).[1c]

(3) (a) Arai, T.; Takahashi, K.; Kubo, A.; Nakahara, S. *Experientia* **1980**, *36*, 1025–1026. (b) Arai, T.; Takahashi, K.; Ishiguro, K.; Mikami, Y. *Gann.* **1980**, *71*, 790–796. (c) Ishiguro, K.; Sakiyama, S.; Takahashi, K.; Arai, T. *Biochemistry* **1978**, *17*, 2545–2550. (d) Haruyama, H.; Kurihara, H.; Kondo, M. *Chem. Pharm. Bull.* **1985**, *33*, 905–915.

(4) Recently, we completed synthesis of the 1,5-imino-3-benzazocine derivative, which is the skeleton of the "right half" of **1**, by using a *p*-methoxybenzyl group as the amide-protecting group: Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S. *Chem. Pharm. Bull.* **1988**, *36*, 2607–2614.

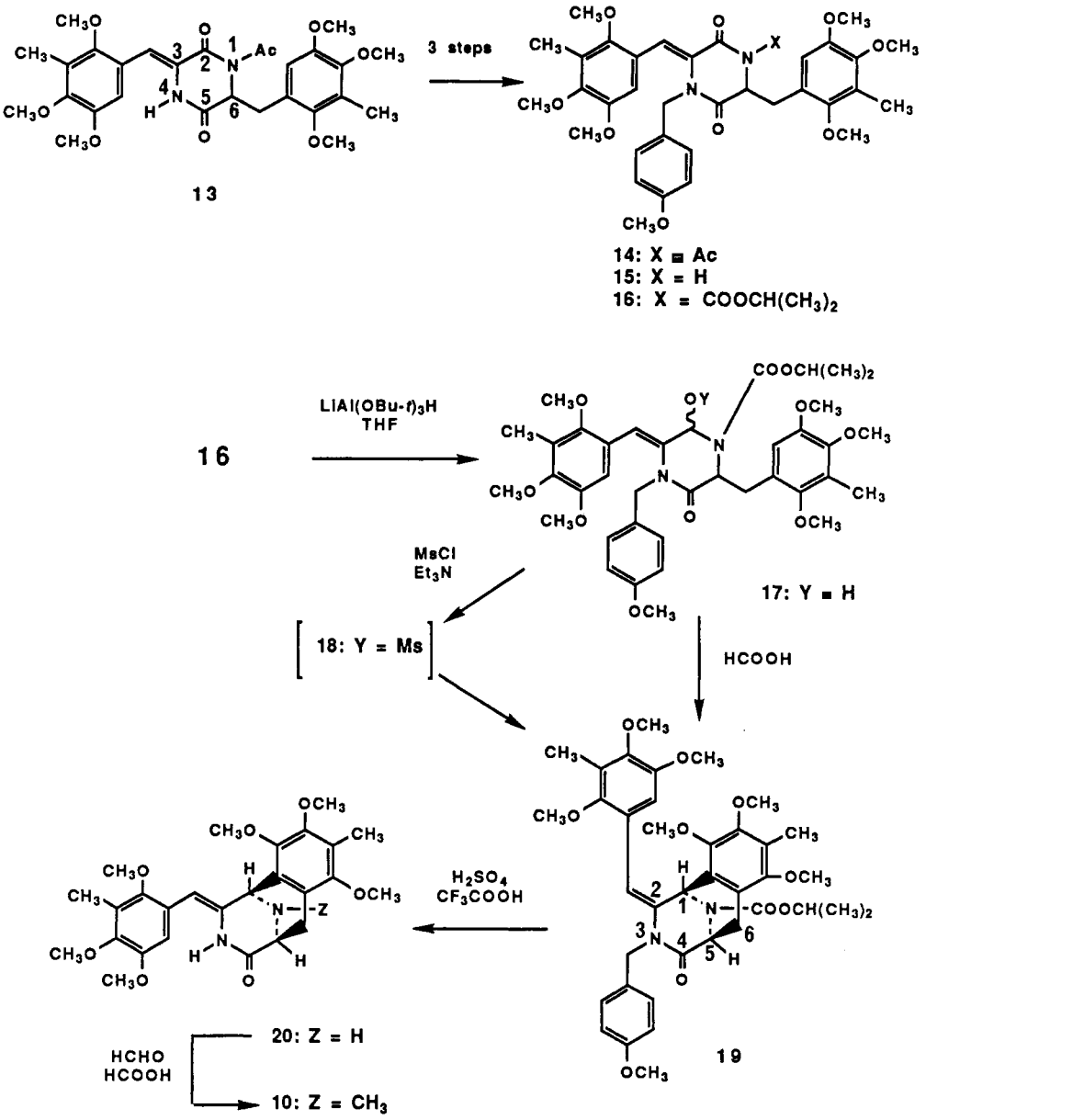
(5) Kubo, A.; Saito, N.; Yamato, H.; Kawakami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525–2532.

(6) We previously reported that after treatment of allylic alcohol **i** with formic acid at 60 °C no cyclized compound could be isolated.[1c] Here, cyclization of **i** was effected by nonacidic conditions to afford the corresponding tricyclic lactam derivative in 71.4% yield.



i

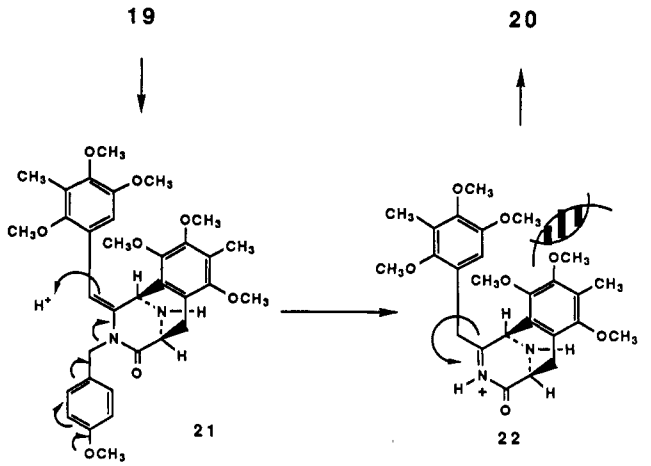
Scheme II



We then studied the conversion of **19** into the secondary amide **10**. Deprotection of **19** with trifluoroacetic acid and H_2SO_4 gave the secondary amide **20** in 72% yield. A probable mechanistic pathway for the formation of *Z*-secondary amide **20** from the *E*-tertiary amide **19** is shown in Scheme III. Methylation of **20** with formaldehyde and formic acid at 70 °C for 1 h gave the tricyclic lactam **10** in 80% yield. The *Z* stereochemical assignments for **20** and **10** are based on ^1H NMR and ^{13}C NMR spectral evidence.[7]

In summary, a direct synthesis of the tricyclic lactam **10** has been accomplished. Efforts to improve the efficiency of the sequence and apply it to the total synthesis of saframycin A (**1**) are now being made.

Scheme III



Experimental Section

All melting points were determined with a Yanagimoto micromelting-point apparatus and are uncorrected. UV spectra were determined in methanol. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. All reactions were conducted under an argon atmosphere. Dry solvents

(7) The alkylation of **10** (NaH, BnBr, DMF, room temperature) affords the *N*-benzyl compound in 59% yield. The ^1H NMR spectrum of this compound displayed H-1 as a singlet at δ 4.55, where as the ^1H NMR spectrum of **11** had δ 5.41.[3c] The signal of the C-1 carbon in the *N*-benzyl compound of **10** appeared at 60.7 ppm, which was at lower field than that of **11** (52.6 ppm).

and reagents were obtained by using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was performed with a rotary evaporator and finally under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (70–230 mesh).

(*Z*)-4-[(4-Methoxyphenyl)methyl]-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (15). Sodium hydride (60% oil dispersion, washed with dry hexane three times, 290 mg, 12.1 mmol) was added to a stirred solution of **13**[5] (5.973 g, 11 mmol) in dry DMF (80 mL), and stirring was continued for 30 min at 0 °C. 4-Methoxybenzyl chloride (1.89 g, 12.1 mmol) in dry DMF (20 mL) was added during 20 min, and the reaction mixture was stirred for 2 h at 25 °C. The reaction mixture was concentrated in vacuo, and the residue was diluted with water (50 mL) and extracted with benzene (100 mL × 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to furnish **14** (7.28 g, 100%) as a pale yellow oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization from benzene–ether to give pure **14** as colorless prisms: mp 155–156.5 °C; IR (KBr) 1725, 1715, 1700, 1635 cm^{-1}; UV λ_{max} (log ϵ) 222 (4.52), 282 (3.91), 345 (4.09) nm; ^1H NMR δ 1.96 (3 H, s, Ar CH_3), 2.21 (3 H, s, Ar CH_3), 2.52 (3 H, s, $COCH_3$), 3.17 (1 H, dd, J = 13, 8 Hz, Ar CH), 3.21 (1 H, dd, J = 13, 6 Hz, Ar CH), 3.55, 3.59, 3.59, 3.59, 3.72, 3.79, 3.95 (each 3 H, s, OCH_3), 4.14 (1 H, d, J = 15 Hz, NCH), 5.25 (1 H, d, J = 15 Hz, NCH), 5.46 (1 H, dd, J = 8, 6 Hz, H-6), 6.48 (1 H, s), 6.69 (2 H, d, J = 9 Hz), 6.82 (2 H, d, J = 9 Hz), 6.85 (1 H, s), 7.36 (1 H, s); MS, m/z (rel intensity) 662 (M^+, 17), 589 (8), 196 (13), 195 (100), 165 (9), 150 (16), 121 (86). Anal. Calcd for $C_{36}H_{42}N_2O_{10}$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.28; H, 6.42; N, 4.19.

Hydrazine monohydrate (5 mL) was added to a stirred solution of the crude **14** (7.28 g, 11 mmol) in dry DMF (80 mL), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to give **15** as a colorless solid, recrystallization of which from acetone afforded pure **15** (5.852 g, 85.8% from **13**) as colorless prisms: mp 145–147 °C; IR (KBr) 3350 br, 1675, 1620 cm^{-1}; UV λ_{max} (log ϵ) 222 (4.52), 284 (4.09), 324 (4.12) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.23 (3 H, s, Ar CH_3), 3.08 (1 H, dd, J = 14, 9 Hz, Ar CH), 3.33 (1 H, dd, J = 14, 4 Hz, Ar CH), 3.55, 3.70, 3.71, 3.73, 3.77, 3.85, 3.86 (each 3 H, s, OCH_3), 4.35 (1 H, ddd, J = 9, 5, 2 Hz, H-6), 4.61 (1 H, d, J = 15 Hz, NCH), 4.76 (1 H, d, J = 15 Hz, NCH), 6.62 (1 H, s), 6.67 (1 H, s), 6.69 (2 H, d, J = 9 Hz), 6.82 (1 H, br s, NH), 6.84 (2 H, d, J = 9 Hz), 7.15 (1 H, s); ^{13}C NMR δ 9.5 (q), 9.8 (q), 33.0 (t), 47.1 (t), 55.1 (q), 56.0 (q), 56.2 (q), 56.2 (d), 60.1 (q), 60.4 (q), 60.8 (q), 61.3 (q), 110.7 (d), 112.0 (d), 113.8 (d), 117.6 (d), 121.8 (s), 123.5 (s), 125.8 (s), 125.9 (s), 128.7 (s), 128.8 (d), 129.7 (s), 147.5 (s), 149.0 (s), 149.2 (s), 149.5 (s), 150.9 (s), 152.1 (s), 158.9 (s), 165.0 (s), 167.5 (s); MS, m/z (rel intensity) 620 (M^+, 12), 590 (29), 589 (79), 196 (12), 195 (97), 165 (11), 121 (100). Anal. Calcd for $C_{34}H_{40}N_2O_9$: C, 65.79; H, 6.50; N, 4.51. Found: C, 65.72; H, 6.58; N, 4.40.

(*Z*)-1-[(Isopropyloxy)carbonyl]-4-[(4-methoxyphenyl)methyl]-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-2,5-piperazinedione (16). The same procedure as described reported previously[1c] but using **15** (4.34 g, 7 mmol) afforded a crude residue. Recrystallization from ether gave pure **16** (4.51 g, 91%) as colorless prisms: mp 136–137.5 °C; IR (KBr) 1745, 1730, 1710 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.47), 284 (3.91), 340 (4.05) nm; ^1H NMR δ 1.24 (3 H, d, J = 6 Hz, $CHCH_3$), 1.31 (3 H, d, J = 6 Hz, $CHCH_3$), 2.02 (3 H, s, Ar CH_3), 2.21 (3 H, s, Ar CH_3), 3.21 (1 H, dd, J = 13, 7 Hz, Ar CH), 3.26 (1 H, dd, J = 13, 7 Hz, Ar CH), 3.55, 3.63, 3.64, 3.72, 3.80, 3.88, 3.93 (each 3 H, s, OCH_3), 4.13 (1 H, d, J = 15 Hz, NCH), 5.02 (1 H, sep, J = 6 Hz, OCH), 5.18 (1 H, dd, J = 7, 7 Hz, H-6), 5.20 (1 H, d, J = 15 Hz, NCH), 6.51 (1 H, s), 6.69 (2 H, d, J = 9 Hz), 6.81 (1 H, s), 6.84 (2 H, d, J = 9 Hz), 7.28 (1 H, s); MS, m/z (rel intensity) 706 (M^+, 11), 675 (18), 589 (23), 196 (12), 195 (100), 121 (83). Anal. Calcd for $C_{38}H_{46}N_2O_{11}$: C, 64.57; H, 6.56; N, 3.96. Found: C, 64.46; H, 6.64; N, 3.90.

(*E*)-3-[(4-Methoxyphenyl)methyl]-2-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Isopropyl Ester (19). Method A. A stirred solution of **16** (3.53 g, 5 mmol) in dry THF (80 mL) was cooled with ice–water, and lithium tri-*tert*-butoxyaluminum hydride (5.09 g, 20 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (3 mL). The reaction mixture was filtered through a Celite pad, and the filtrates were concentrated in vacuo. The crude diastereomeric mixture of the allylic alcohol **17** (along with **15**) obtained was used for the next step without isolation. A solution of the above mixture (**17** and **15**) in formic acid (30 mL) was heated at 60 °C for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with chloroform (100 mL × 3). The combined organic extracts were washed with 10% NH_4OH (100 mL) and then with water (50 mL), dried, and concentrated in vacuo to give the residue. Chromatography on a silica gel (80 g) column with hexane–AcOEt (3:1–2:1) as the eluent gave **19** as a colorless solid, recrystallization of which from AcOEt–ether afforded pure **19** (1.43 g, 41.4%) as colorless prisms. Further elution with AcOEt–MeOH (8:1) gave **19** (322 mg, 10.4%) as colorless prisms whose spectra are identical with those of an authentic sample obtained as above.

Method B. A stirred solution of **16** (1.412 g, 2 mmol) in dry THF (20 mL) was cooled with ice–water, and lithium tri-*tert*-butoxyaluminum hydride (2.03 g, 8 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was subjected to the same workup as above to give the crude diastereomeric mixture of the allylic alcohol **17** (along with **15**). A solution of the above mixture (**17** and **15**) and triethylamine (1 mL, 7.2 mmol) in dry dichloromethane (40 mL) was cooled with ice–water, and methanesulfonyl chloride (0.56 mL, 7.2 mmol) was added dropwise over 10 min. The solution was heated under reflux for 20 h. The organic layer was washed with 1 N HCl (20 mL × 2), and then with water (30 mL), dried, and concentrated in vacuo. Chromatography of the residue on a silica gel (60 g) column with hexane–AcOEt (5:1–2:1) as the eluent gave **19** as colorless solid, recrystallization of which from AcOEt–ether afforded pure **19** (969 mg, 70.2%) as colorless prisms. Further elution with AcOEt–MeOH (8:1) gave **15** (131 mg, 10.6%) as colorless prisms. Compound **19**: mp 180–181.5 °C; IR (KBr) 1705, 1670, 1640 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.38), 275 (4.11), 302 (3.88) nm; ^1H NMR δ 1.27 (3 H, d, J = 6 Hz, $CHCH_3$), 1.32 (3 H, d, J = 6 Hz, $CHCH_3$), 2.17 (3 H, s, Ar CH_3), 2.18 (3 H, s, Ar CH_3), 2.98, 2.98 (each 3 H, s, OCH_3), 3.06 (1 H, dd, J = 17, 6 Hz, H-6α), 3.38 (1 H, d, J = 17 Hz, H-6β), 3.45, 3.68, 3.69, 3.80, 3.99 (each 3 H, s, OCH_3), 4.50 (1 H, d, J = 16 Hz, NCH), 5.01 (1 H, sep, J = 6 Hz, $CHCH_3$), 5.22 (1 H, d, J = 6 Hz, H-5), 5.56 (1 H, d, J = 16 Hz, NCH), 6.11 (1 H, s, C=CH), 6.56 (2 H, d, J = 9 Hz), 6.63 (2 H, d, J = 9 Hz), 6.75 (1 H, s, H-1), 7.50 (1 H, s); ^{13}C NMR δ 9.3 (q), 9.3 (q), 22.2 (q), 22.2 (q), 28.2 (t), 43.4 (t), 45.9 (d), 53.5 (d), 55.2 (q), 56.6 (q), 59.1 (q), 59.7 (q), 59.9 (q), 60.1 (q), 60.4 (q), 69.6 (d), 107.7 (d), 110.4 (d), 113.8 (d), 121.8 (s), 124.8 (s), 125.1 (s), 125.3 (s), 125.5 (s), 127.5 (d), 128.5 (s), 134.8 (s), 146.5 (s), 146.9 (s), 149.2 (s), 150.3 (s), 150.8 (s), 152.7 (s), 152.9 (s), 158.5 (s), 168.3 (s); MS, m/z (rel intensity) 690 (M^+, 43), 321 (18), 320 (10), 279 (17), 278 (17), 235 (11), 234 (50), 204 (17), 195 (10), 121 (100). Anal. Calcd for $C_{38}H_{46}N_2O_{10}$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.16; H, 6.84; N, 3.99.

(*Z*)-2-[(2,4,5-Trimethoxy-3-methylphenyl)methylene]-7,9,10-trimethoxy-8-methyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (20). Concentrated H_2SO_4 (2 mL) was added to a stirred solution of **19** (1.38 g, 2 mmol) in trifluoroacetic acid (40 mL), and the resulting solution was stirred for 24 h at 25 °C. The reaction mixture was poured into water (50 mL) and extracted with dichloromethane (100 mL × 3). The combined extracts were washed with 10% NH_4OH (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from AcOEt–ether gave **20** (741.2 mg, 71.6%) as colorless prisms: mp 125.5–127 °C; IR (KBr) 3290, 1675 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.42), 276 (4.26), 302 (4.09) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.19 (3 H, s, Ar CH_3), 2.25 (1 H, br s, amine NH), 3.09 (1 H, dd, J = 17, 7 Hz, H-6α), 3.18 (1 H, dd, J = 17, 2 Hz, H-6β), 3.40, 3.69, 3.72, 3.78, 3.83, 3.91 (each 3 H, s, OCH_3), 4.03 (1 H, dd, J = 7, 2 Hz, H-5), 4.98 (1 H, s, H-1), 5.78 (1 H, s, C=CH), 6.57 (1 H, s), 8.41 (1 H, s, amide NH); ^{13}C NMR δ 9.3 (q), 9.3 (q), 27.6 (t), 50.0 (d), 52.3 (d), 56.0 (q), 59.8 (q), 59.8 (q), 60.1 (q), 60.3 (q), 60.3 (q), 101.9 (d), 110.8 (d), 121.6 (s), 122.7 (s), 124.7 (s), 126.2 (s), 126.3 (s), 136.3 (s), 146.3 (s), 147.3 (s), 148.9 (s), 149.4 (s), 149.9 (s), 152.5 (s), 170.9 (s); MS, m/z (rel intensity) 484 (M^+, 66), 235

(27), 234 (100), 223 (32), 208 (13), 206 (14), 204 (23). Anal. Calcd for $C_{28}H_{32}N_2O_7$: C, 64.45; H, 6.66; N, 5.78. Found: C, 64.13; H, 6.83; N, 5.50.

(Z)-2-[(2,4,5-Trimethoxy-3-methylphenyl)methylene]-7,9,10-trimethoxy-8,11-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (10). Formaldehyde (37% solution water, 0.92 mL) was added to a stirred solution of **20** (556.3 mg, 1.14 mmol) in formic acid (2.16 mL) at 50 °C. After being stirred for 1 h at 70 °C, the reaction mixture was poured into water (40 mL) and extracted with chloroform (30 mL × 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), and water (20 mL × 2), dried, and concentrated in vacuo to give a solid, recrystallization of which from AcOEt–ether gave **10** (461.5 mg, 80%) as colorless prisms: mp 200.5–202 °C; IR (KBr) 3380, 1695, 1670 cm^{-1}; UV λ_{max} (log ϵ) 224 (4.44), 277 (4.29), 302 (4.11) nm; ^1H NMR δ 2.17 (3 H, s, Ar CH_3), 2.18 (3 H, s, Ar CH_3), 2.60 (3 H, s, NCH_3), 3.16 (2 H, br, H-6α and H-6β), 3.41 (3 H, s, OCH_3), 3.63 (1 H, br d, H-5), 3.68, 3.72, 3.78, 3.83, 3.91 (each 3 H, s, OCH_3), 4.63 (1 H, s, H-1), 5.89 (1 H, s, C=CH), 6.56 (1 H, s), 8.41 (1 H, s, amide NH); ^{13}C NMR δ 9.3 (q), 9.5 (q), 27.6 (t), 41.6 (q), 56.1 (q), 56.8 (d), 59.2 (d), 59.8 (q), 59.9 (q), 60.2 (q), 60.3 (q), 60.3 (q), 104.5 (d), 110.0 (d), 121.3 (s), 122.7 (s), 124.6 (s), 126.3 (s), 126.3 (s), 133.7 (s), 146.3 (s), 147.4 (s), 149.0 (s), 149.4 (s), 150.0 (s), 152.5 (s), 169.7 (s); MS, m/z (rel intensity) 498 (M^+, 23), 249 (20), 248 (100), 218 (15). Anal. Calcd for $C_{27}H_{34}N_2O_7 \cdot {}^1/_5H_2O$: C, 64.58; H, 6.90; N, 5.58. Found: C, 64.55; H, 7.00; N, 5.35.

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Facile Transformation of Substituted Allyl Malonates to Monocarboxylic Acids and Esters by the Reaction with Ammonium Formate Catalyzed by Palladium Complexes

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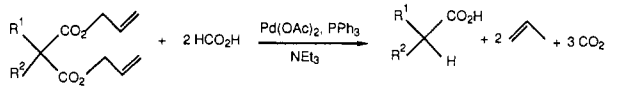
Malonic esters are important intermediates for the synthesis of substituted carboxylic acids or esters. In the malonate method, at first methyl or ethyl malonate is mono- or dialkylated. The hydrolysis of the substituted esters followed by thermal decarboxylation affords substituted carboxylic acids. Although the method is synthetically useful, one drawback is the difficulty in hydrolyzing the substituted malonic esters. Usually the hydrolysis is carried out under rather drastic conditions using a strong base or acid at a high temperature. Therefore, the method cannot be applied to malonates with labile functional groups. To overcome this difficulty, Krapcho and co-workers introduced a good method of the dealkoxycarbonylation to afford mono esters.[1] Substituted malonates undergo the dealkoxycarbonylation to afford monoesters by refluxing in wet DMSO or DMF with an excess of inorganic salts such as NaCN, NaCl, LiI, or LiCl.[2,3] In addition, Ho reported that malonate esters can be converted to carboxylic acids by treatment with iodotrimethylsilane at 100 °C.[4] Also monoesters are obtained by heating substituted malonates with 1 equiv of boric acid at 170–190 °C.[5] In these methods, excess amounts of inorganic salts are required, and the reactions are carried out at somewhat high temperatures.

We now wish to report a simple method for the conversion of substituted malonate esters into monocarboxylic acids or esters under mild conditions. The present method is an extension of our method for the facile hydrogenolysis of allylic esters with tertiary amine salts (typically triethylamine) of formic acid, catalyzed by a palladium phosphine complex, which proceeds with evolution of carbon dioxide and propylene.[6,7]

This reaction proceeds under nearly neutral conditions at lower temperature without attacking labile functional groups. The method can be carried out easily by refluxing a dioxane solution of diallyl esters of mono- or disubstituted malonic acids and slight excesses of triethylamine and formic acid containing catalytic amounts of palladium acetate and triphenylphosphine for several hours. After workup, substituted carboxylic acids are isolated in good yields (Scheme I). Some examples are shown in Table I. When the reaction is carried out at room temperature, only hydrogenolysis takes place to afford substituted malonic acids.

Also, the preparation of monoesters can be carried out. Allyl ethyl malonate was prepared and mono- or dialkylated. The products were subjected to the reaction with HCO_2H–NEt_3 in the presence of the palladium catalyst. In this way ethyl esters were obtained as shown in Scheme II. Some results are given in Table II.

Scheme I



Scheme II

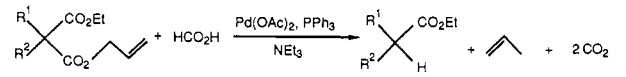
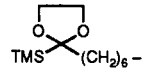


Table I. Preparation of Monocarboxylic Acids[a]

run	R^1	R^2	yield,[b] %
1	n-C_6H_{13}	H	80
2	n-C_6H_{13}	$PhCH_2$	83
3	t-$BuPh_2SiO(CH_2)_4$	H	67
4	$AcO(CH_2)_4$	$PhCH_2$	86

[a] Malonate 0.7 mmol, $Pd(OAc)_2$ 2%, PPh_3 8%, HCO_2H 2.5 equiv, NEt_3 3.3 equiv, dioxane 6 mL, reflux 5 h. [b] Isolated yield.

Table II. Preparation of Monoesters[a]

run	R^1	R^2	time, h	yield,[b] %
5	THPO–$(CH_2)_4$	H	7.0	70
6	THPO–$(CH_2)_4$	$PhCH_2$	7.5	90
7		EtO_2CCH_2	5.0	96

[a] Malonate 0.7 mmol, $Pd(OAc)_2$ 2%, PPh_3 8%, HCO_2H 1.25 equiv, NEt_3 1.30 equiv, dioxane 6 mL, reflux. [b] Isolated yield.

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