Oxazolidin-2-ones from Allylic Amines by means of Iodine and Carbonate Anion on Polymeric Support. A Convenient Synthesis of (±)-Propranolol

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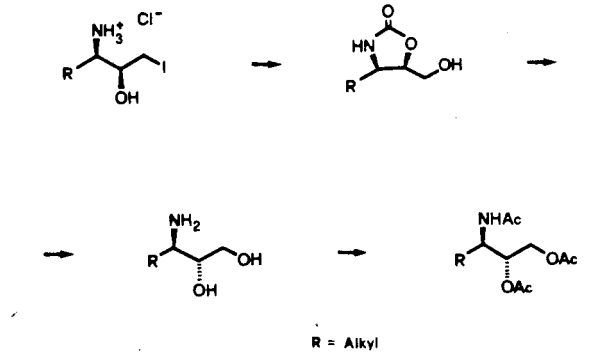
A new polymeric reagent was obtained by adsorbing iodine on the resin Amberlyst A 26 in the CO_3^{2-} form. By treating at room temperature a solution of allylic amines hydrochlorides **4** or free amine **5** with this polymeric reagent, 5-(iodomethyl)oxazolidin-2-ones **6** were obtained in very good yield. Iodine displacement, base hydrolysis, and full acetylation gave **8**, while deiodination followed by base hydrolysis and full acetylation afforded **10**, respectively. The potential utility of the new polymeric reagent was demonstrated by a short, effective synthesis of (±)-propranolol (**17**).

High asymmetric induction may be achieved in acyclic systems through intermediate ring formation.[1] In this area we have recently developed some new methods for a regio- and stereocontrolled functionalization of allylic and homoallylic carbonates, imidates, and amides.[2] In a preceding communication we described the synthesis of 5-(hydroxymethyl)oxazolidin-2-ones, starting from iodo amino alcohol hydrochlorides (Scheme I). This reaction was carried out with Amberlyst A 26 in the CO_3^{2-} form in methanol, and successive basic hydrolysis and acetylation afforded 3-amino 1,2-diol triacetates through the insertion of a carbon dioxide molecule.[3] The capability of the amine to bind a carbon dioxide molecule led us to realize a new polymeric reagent that was able to release contemporaneously carbon dioxide and iodine.

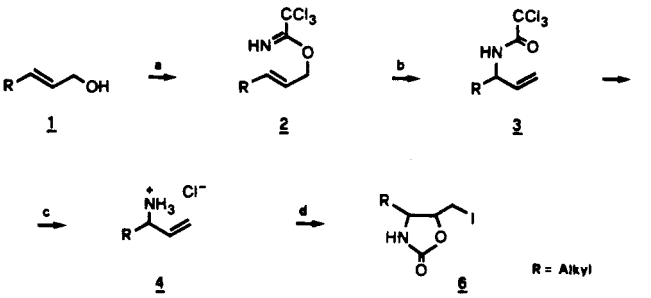
We wish now to report a one-step procedure leading to the 5-(iodomethyl)oxazolidin-2-ones **6**, a new class of compounds that allows an easy access to 3-amino 1,2-diol and amino alcohol moieties, starting from allylic amine hydrochlorides **4** or free amine **5**. These amines were readily prepared by thermal rearrangement of allylic trichloroacetimidates **2**, followed by basic hydrolysis of the corresponding trichloroacetamides **3**[4] (Scheme II).

Allylic amine hydrochlorides **4** or the free amine **5**[5] were treated with the reagent obtained by adsorbing iodine on the resin Amberlyst A 26 in the CO_3^{2-} form.[6] Treatment at room temperature of a $CHCl_3$ solution of **4** or **5** (1 equiv) with this polymeric reagent (2 equiv) for 10 h at room temperature afforded in very high yield a diastereomeric mixture of 5-(iodomethyl)oxazolidin-2-ones **6a–f**, as determined by ^{13}C spectra and GLC analysis of the reaction mixtures. The stereostructures were assigned on the basis of the ^1H NMR coupling constants ($J_{4,5\,cis}$ = 7.5 Hz and $J_{4,5\,trans}$ = 4.5 Hz)[7] and the ^{13}C chemical shifts of vicinal carbons, which are more shielded in the cis isomers.[8] We have indeed observed that for this type of compound, the ^{13}C chemical shift of CH_2I is a valuable tool, the δ_C ranging between −0.5 and +1.0 for the cis isomer, and between 7.5 and 8.5 for the trans one (Table I).

Scheme I



Scheme II[a]



[a] (a) Catalyst NaH/THF/CCl_3CN; (b) refluxing toluene; (c) 4 M NaOH, then 2 N HCl; (d) Amberlyst A 26 in the CO_3^{2-} form/I_2, $CHCl_3$, room temperature.

The regioselection of this reaction is worthy of comment: through a 5-exo ring closure, only five-membered rings were formed, whose structures were assigned from the analysis of their IR spectra (characteristic absorption at 1750 cm^{-1}).[9] This expected result was in agreement with a nucleophilic attack on the intermediate iodonium ion at the more stable incipient secondary cation.[10]

Moreover, when R = C_3H_7 and R = CH_2OTHP (**6a** and **6f**), only a moderate diastereoselection was observed; when R is CH_2OCH_2Ph, the cis–trans ratio raised to 30:70 in favor of the trans isomer **6b**. When R = CH_2OH, the trans oxazolidin-2-one was obtained with higher diastereoselection, the cis–trans ratio being 7:93 (**6c**), as shown by ^{13}C NMR spectrum, where the major isomer had a resonance

(1) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) Bartlett, P. A. In "Asymmetric Synthesis", 1st ed.; Morrison, J. D. Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 6 and references cited therein.

(2) (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 466. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626. (c) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1308. (d) Cardillo, G.; Orena, M.; Sandri, S. *Ibid.* **1983**, 1489.

(3) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1985**, *41*, 163.

(4) (a) Overman, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (b) Yamamoto, Y.; Shimoda, H.; Oda, J.; Ynouye, Y. *Bull. Soc. Jpn.* **1976**, *49*, 3247.

(5) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.

(6) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Synthesis* **1981**, 793.

(7) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680.

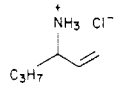
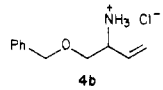
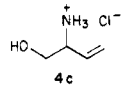
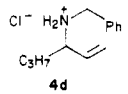
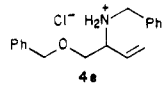
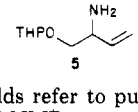
(8) Schneider, H. J.; Nguyen-Ba, N.; Thomas, R. *Tetrahedron* **1982**, *38*, 2327.

(9) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654.

(10) For the cyclization of allylic urethanes, see: (a) Pauls, H. W.; Fraser-Reid, B. J. *J. Am. Chem. Soc.* **1980**, *102*, 3956. (b) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, 619. (c) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, 4887.

0022-3263/86/1951-0713$01.50/0

Table I. Synthesis of 5-(Iodomethyl)oxazolidin-2-ones 6

substrate	product 6 (yield[a] %)	diastereomeric ratio[b] (cis:trans)
 4a	**6a** (95)	55:45
 4b	**6b** (94)	30:70
 4c	**6c** (80)	7:93
 4d	**6d** (95)	30:70
 4e	**6e** (90)	1:99
 5	**6f** (95)	40:60

[a] Yields refer to pure isolated products. [b] Determined by GLC and ^{13}C NMR.

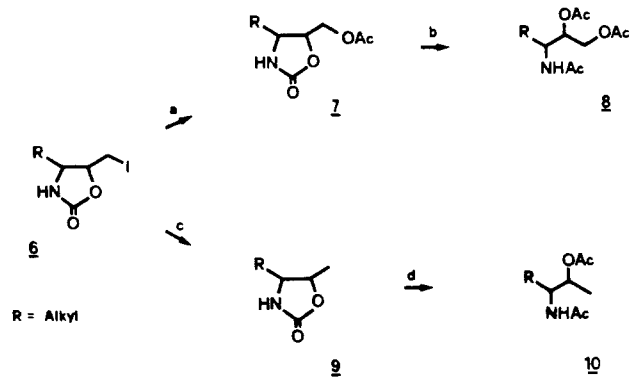
at δ 8.3 (CH_2I) and the minor one at δ 0.2 (CH_2I). The trans configuration of the major isomer of **6c** was further confirmed by ^1H NMR analysis using the double irradiation technique. The value of 2 Hz for the $J_{4,5}$ is consistent with the assigned trans configuration.[11] This result was certainly connected with the presence of a free hydroxyl group.

Since it was already reported[12] that a *N*-benzyl substituent plays an important control on the iodocyclocarbamation, leading to the thermodynamically more stable trans isomer, in order to enhance the diastereoselection, we prepared *N*-benzylallylamine hydrochlorides **4d** and **4e** and cyclized them under the kinetic conditions described above. We obtained a large change in the cis–trans ratios of **6d** (30:70) and **6e** (1:99), as compared with the corresponding ratios of **6a** (55:45) and **6b** (30:70), respectively. With the kinetic experimental conditions, these data support the important role of the substituent on the nitrogen during the cyclization.

In an attempt to obtain 3-amino 1,2-diol derivatives, the iodine displacement in **6a–c** was performed with Amberlyst A 26 in the AcO^- form in refluxing benzene.[13] Successive basic treatment and full acetylation gave the triacetates **8a,b** (Scheme III).

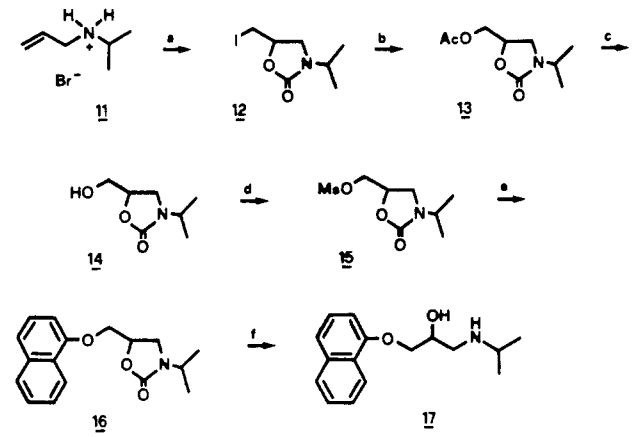
Two methods for the reductive cleavage of the C–I bond were also examined, with the aim to prepare amino alcohols. Treatment of **6a–c** (1 equiv) with $LiAlH_4$ (2 equiv) in dry THF for 3 h at room temperature gave the 5-methyloxazolidin-2-ones **9a–c** in good yield (method A). Alternatively, treatment of **6a–c** (1 equiv) with tri-*n*-butyltin hydride (2 equiv) in boiling ethanol for 12 h in the presence of the radical initiator 2,2′-azobis(2-methylpropanenitrile) resulted in the isolation of compounds **9a–c** in slightly better yield (method B).[14] The conversion to the diacetates **10a,b** was conveniently realized by basic hydrolytic cleavage followed by full acetylation.

Scheme III



[a] (a) Amberlyst A 26 in the AcO^- form, refluxing benzene; (b) 4 N KOH, then Ac_2O/pyridine; (c) $LiAlH_4$ in THF (method A) or Bu_3SnH in EtOH (method B); (d) 4 N KOH, then Ac_2O/pyridine.

Scheme IV



[a] Amberlyst A 26 in the CO_3^{2-} form/iodine/$CHCl_3$; (b) Amberlyst A 26 in the AcO^- form; (c) K_2CO_3 in EtOH; (d) $CH_3SO_2Cl/Et_3N/CH_2Cl_2$; (e) Amberlyst A 26 in the α-naphtolate form; (f) 4 N KOH.

To demonstrate the value of this novel cyclization process and its potential applicability to the construction of compounds with biological activity, propranolol (**17**), a β-adrenergic receptor antagonist,[15] was synthesized (Scheme IV).

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or sodium benzophenone immediately prior to use. All reactions involving organometallic reagents were carried out under an argon atmosphere. Melting points (Pyrex capillary) were determined on a Buchi 510 hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 682 spectrophotometer either on films or, for solids, on Nujol mulls. ^1H NMR spectra were recorded on either a Perkin-Elmer R 12B (60 MHz) or a Varian XL-100 (100 MHz) spectrometer with tetramethylsilane as internal reference. ^{13}C NMR spectra (20 MHz) were recorded with a Varian FT 80-A spectrometer. All chemical shifts were measured relative to tetramethylsilane δ_C 0. Mass spectra were obtained with a double-focusing Varian

(11) Kagan, H. B. "Stereochemistry"; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1, p 89.
(12) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, 5079.
(13) Cainelli, G.; Manescalchi, F. *Synthesis* **1975**, 723.
(14) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.
(15) (a) Crowter, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009. (b) Shtacher, G.; Rubenstein, R. *Ibid.* **1978**, *21*, 678. (c) Danilewics, J.; Kemp, J. *Ibid.* **1979**, *22*, 2943. (d) Weinstock, L. M.; Mulvey, D. M.; Tull, R. *J. Org. Chem.* **1976**, *41*, 3121. (e) Baldwin, J. J.; Hirschmann, R.; Lumma, P. K.; Lumma, W. C.; Ponticello, G. S.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1977**, *20*, 1024. (f) Bäckvall, J. E.; Bystrom, S. E. *J. Org. Chem.* **1982**, *47*, 1126.
(16) Cardillo, G.; Contento, M.; Sandri, S.; Panunzio, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1729.

MAT 112 instrument at an ionizing voltage of 70 eV. Mass spectral data (MS) are tabulated as m/e values. Analytical GLC was carried out on a Carlo Erba capillary gas chromatograph (Fractovap 4160) equipped with a SE-52 flexible glass capillary column (25 m × 0.3 mm i.d.; carrier gas He; p_{He} 0.6 kg cm^{-2}). Chromatograms, peak areas, and retention times were obtained by using a Perkin-Elmer Sigma 10 data processor. TLC and column chromatography were carried out on Kieselgel GF_{254} (Merck). Solvent ratios are in volume before mixing. Solutions were dried over anhydrous magnesium sulphate.

General Procedure for the Preparation of Allylamines Hydrochlorides (4a–c). A solution of the allylic alcohol 1 (40 mmol) in dry THF (50 mL) under argon was added at 0 °C to a stirred suspension of NaH (50% in mineral oil; 400 mg; 8 mmol; previously washed with dry pentane) in dry THF (30 mL). After 1 h the resulting mixture was added dropwise at 0 °C to a solution of trichloroacetonitrile (6.4 g; 44 mmol) in dry THF (30 mL). The solution was stirred for 1.5 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in decahydronaphthalene (50 mL), and the solution was refluxed for 12 h. The mixture was directly chromatographed through silica gel, with cyclohexane as eluant to remove decahydronaphthalene and then with cyclohexane–ethyl acetate (95:5), to afford the trichloroacetamides **3** as a clear oil, which were dissolved in methanol (5 mL) and hydrolyzed with a 4 N NaOH solution (40 mL) at 60 °C for 5 h. After extraction with ether (2 × 100 mL) and a washing of the combined extracts with 2 N HCl solution (25 mL), the aqueous solution was stripped off in vacuo, affording the hydrochlorides **4a–e** in very high yields as colorless oils.

General Procedure for the Preparation of Allylamines Hydrochlorides (4d–e). The free allylic amines (20 mmol) (obtained from the corresponding hydrochlorides **3a,b** by washing with 2 N NaOH solution (20 mL)) and benzyl chloride (20 mmol; 2.6 g) were refluxed for 30 h in benzene, and then the solvent was stripped off in vacuo. The crude hydrochloride was washed with ether and directly used without further purification.

3-Amino-1-hexene hydrochloride (4a): 80%; IR 3400, 1600, 940 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.95 (t, 3 H), 1.2–2.0 (m, 4 H), 3.6–4.2 (m, 1 H), 4.8 (br s, 3 H, NH_3^+), 5.2–6.3 (m, 3 H).

3-Amino-4-(benzyloxy)-1-butene hydrochloride (4b): 82%; IR 3400, 1620, 950 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.6 (m, 2 H), 3.8–4.1 (m, 1 H), 4.6 (s, 2 H), 5.3 (br s, 3 H, NH_3^+), 5.1–6.2 (m, 3 H), 7.4 (m, 5 H_{Ar}).

2-Amino-3-buten-1-ol hydrochloride (4c): 79%; IR 3300, 1610, 1570, 950 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.6 (d, 2 H), 3.8–4.2 (m, 1 H), 4.8 (br s, 4 H, NH_3^+ + OH), 5.0–6.2 (m, 3 H).

3-(*N*-Benzylamino)-1-hexene hydrochloride (4d): 83%; IR 3400, 950 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 0.95 (t, 3 H), 1.2–2.0 (m, 4 H), 3.95 (m, 2 H), 4.0–4.4 (m, 1 H), 4.85 (br s, 2 H, NH_2^+), 5.2–6.3 (m, 3 H), 7.2–7.9 (m, 5 H_{Ar}).

3-(*N*-Benzylamino)-4-(benzyloxy)-1-butene hydrochloride (4e): 80%; IR 3350, 945 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 3.95 (m, 2 H), 4.0–4.4 (m, 1 H), 4.55 (s, 2 H), 4.8 (br s, 2 H, NH_2^+), 5.2–6.3 (m, 3 H), 7.2–7.9 (m, 10 H_{Ar}).

3-Amino-4-[((tetrahydro-2-pyranyl)oxy)methyl]-1-butene (5): 82%; IR 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–2.0 (m, 6 H), 3.0–4.1 (m, 7 H), 4.6 (m, 1 H), 5.0–6.1 (m, 3 H).

General Preparation of 5-(Iodomethyl)oxazolidin-2-ones (6a–f). A suspension of Amberlyst A 26 (6 g; ~3.8 mequiv/g) in the CO_3^{2-} form in $CHCl_3$ (30 mL) containing iodine (5 g; 20 mmol) was stirred for 1 h until the color disappeared. A solution of **4a–e** (10 mmol) or **5** (10 mmol) in $CHCl_3$ (10 mL) was then added and the mixture stirred at room temperature for 12 h. The resin was filtered off and the solvent removed under reduced pressure. After column chromatography over silica gel with ethyl acetate as the eluant 5-(iodomethyl)oxazolidin-2-ones **6a–f** were obtained as colorless oils.

5-(Iodomethyl)-4-propyloxazolidin-2-one (6a): 95%; cis–trans ratio 55:45; IR 3260, 1750 cm^{-1}. Cis isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.9 (m, 4 H), 3.35 (d, 2 H, J = 6 Hz), 3.6–4.1 (m, 1 H), 4.9 (q, 1 H; J = 7.5 Hz), 7.3 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 160.0, 80.7, 54.1, 31.8, 19.9, 14.2, 1.0 (CH_2I). Trans isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.9 (m, 4 H), 3.35 (d, 2 H, J = 6 Hz), 3.5–3.9 (m, 1 H), 4.3 (q, 1 H, J = 4 Hz), 7.3 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 159.9, 81.1, 58.9, 38.4, 18.9, 14.2, 8.2 (CH_2I); MS, m/e (relative intensity) 269 (M^+, 2), 226 (4), 182 (3), 142 (4), 113 (10), 88 (100). Anal. Calcd for $C_7H_{12}NO_2I$: C, 31.24; H, 4.49. Found: C, 31.22; H, 4.47.

4-[(Benzyloxy)methyl]-5-(iodomethyl)oxazolidin-2-one (6b): 94%; cis–trans ratio 30:70; IR 3250, 1750 cm^{-1}. Cis isomer: ^{1}H NMR ($CDCl_3$) δ 3.3 (d, 2 H; J = 6 Hz), 3.4–3.6 (m, 2 H), 3.7–4.2 (m, 1 H), 4.5 (s, 2 H), 4.6–5.0 (m, 1 H, J = 7.5 Hz), 6.1 (br s, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) δ 139.0, 129.3, 129.0, 128.7, 80.3, 74.2, 68.5, 56.0, 0.0 (CH_2I). Trans isomer: ^{1}H NMR ($CDCl_3$) δ 3.4 (d, 2 H, J = 6 Hz), 3.5–3.9 (m, 3 H), 4.2–4.5 (m, 1 H, J = 4.5 Hz), 4.6 (s, 2 H), 6.2 (br s, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) δ 139.0, 129.3, 129.0, 128.7, 78.5, 74.2, 72.0, 59.0, 8.0 (CH_2I); MS, m/e (relative intensity) 347 (M^+, 1), 236 (30), 226 (16), 219 (11), 182 (12), 91 (100). Anal. Calcd for $C_{12}H_{14}NO_3I$: C, 41.51; H, 5.24. Found: C, 41.49; H, 5.22.

4-(Hydroxymethyl)-5-(iodomethyl)oxazolidin-2-one (6c): 80%; cis–trans ratio 7:93; IR 3300, 1750 cm^{-1}. Cis isomer: ^{13}C NMR (CD_3OD) δ 160.4, 80.6, 62.1, 57.2, 0.2 (CH_2I). Trans isomer: ^{1}H NMR (CD_3OD) δ 3.5 (d, 2 H, J = 5 Hz), 3.65 (m, 2 H), 3.6–3.9 (m, 1 H), 4.3–4.65 (m, 1 H, J = 5 Hz, J = 2 Hz), 4.8 (br s, 2 H, OH + NH); ^{13}C NMR (CD_3OD) δ 160.4, 78.2, 63.6, 60.6, 8.3 (CH_2I); MS, m/e (relative intensity) 226 (M^+ – CH_2OH, 23), 182 (11), 99 (100). Anal. Calcd for $C_5H_8NO_3I$: C, 23.36; H, 3.13. Found: C, 23.34; H, 3.10.

3-Benzyl-5-(iodomethyl)-4-propyloxazolidin-2-one (6d): 95%; cis–trans ratio 30:70; IR 1750 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 0.9 (t, 3 H), 1.1–1.8 (m, 4 H), 3.4 (d, 2 H, J = 5 Hz), 3.4–3.8 (m, 1 H), 4.0–4.8 (m, 3 H), 7.4 (m, 5 H_{Ar}). Cis isomer: ^{13}C NMR (CD_3COCD_3) δ 136.0, 129.7, 128.3, 127.8, 78.9, 58.6, 47.1, 29.5, 19.7, 14.4, 0.95 (CH_2I). Trans isomer: ^{13}C NMR (CD_3COCD_3) δ 136.0, 129.7, 128.3, 127.8, 77.8, 61.3, 46.9, 34.3, 17.8, 14.3, 8.5 (CH_2I); MS, m/e (relative intensity) 359 (M^+, 2), 316 (4), 146 (53), 91 (100). Anal. Calcd for $C_{14}H_{18}NO_2I$: C, 46.81; H, 5.05. Found: C, 46.79; H, 5.04.

3-Benzyl-4-[(benzyloxy)methyl]-5-(iodomethyl)oxazolidin-2-one (6e): 90%; cis–trans ratio 1:99; IR 1760 cm^{-1}. Trans isomer: ^{1}H NMR (CD_3COCD_3) δ 3.4–4.0 (m, 5 H), 4.0–4.7 (m, 5 H), 7.35 (m, 5 H_{Ar}); ^{13}C NMR (CD_3COCD_3) δ 137.1, 129.7, 129.5, 129.4, 128.9, 76.0, 74.2, 69.1, 62.0, 47.4, 7.9 (CH_2I); MS, m/e (relative intensity) 437 (M^+, 3), 346 (9), 316 (8), 236 (30), 146 (85), 91 (100). Anal. Calcd for $C_{19}H_{20}NO_3I$: C, 52.18; H, 4.61. Found: C, 52.16; H, 4.60.

4-[((Tetrahydro-2-pyranyl)oxy)methyl]-5-(iodomethyl)-oxazolidin-2-one (6f): 95%; cis–trans ratio 40:60; IR 3350, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 6 H), 3.0–4.1 (m, 7 H), 4.2–5.0 (m, 2 H), 6.8 (d, 1 H, NH, J = 9 Hz). Cis isomer: ^{13}C NMR (CD_3OD) δ 100.0, 80.6, 65.9, 63.2, 56.3, 31.5, 26.3, 20.2, –0.4 (CH_2I). Trans isomer: ^{13}C NMR (CD_3OD) δ 100.2, 78.7, 69.6, 63.2, 59.2, 31.5, 26.3, 20.2, 7.7 (CH_2I); MS, m/e (relative intensity) 252 (M^+ – CH_2OTHP, 40), 226 (20), 182 (10), 85 (100). Anal. Calcd for $C_{10}H_{16}NO_4I$: C, 35.20; H, 4.72. Found: C, 34.97; H, 4.70.

General Procedure for the Preparation of 5-(Acetoxymethyl)oxazolidin-2-ones (7a–c). To a solution of 5-(iodomethyl)oxazolidin-2-one **6** (5 mmol) in benzene (20 mL) was added Amberlyst A 26 (5 g; ~3.8 mequiv/g) in the AcO^- form, and the mixture was refluxed for 4 h. The resin was then filtered off and washed with MeOH (20 mL). The solvent was stripped off in vacuo, and the residue was chromatographed over silica gel with cyclohexane–ethyl acetate (7:3) as eluant, to afford 5-(acetoxymethyl)oxazolidin-2-ones **7a–c** as colorless oils.

5-(Acetoxymethyl)-4-propyloxazolidin-2-one (7a): 70%; cis–trans ratio 55:45; IR 3300, 1750 cm^{-1}. Cis isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.8 (m, 4 H), 2.1 (s, 3 H), 3.4–3.7 (m, 1 H), 4.3 (d, 2 H), 4.6–5.0 (m, 1 H), 7.1 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.3, 78.8, 61.9, 54.6, 31.9, 19.6, 18.4, 13.8. Trans isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.8 (m, 4 H), 2.1 (s, 3 H), 3.45–3.8 (m, 1 H), 4.3 (d, 2 H), 4.1–4.6 (m, 1 H), 7.1 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.3, 79.3, 64.2, 54.6, 37.5, 20.7, 18.4, 13.8; MS, m/e (relative intensity) 201 (M^+, 1), 158 (10), 141 (20), 128 (12), 98 (100). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51. Found: C, 53.69; H, 7.50.

5-(Acetoxymethyl)-4-[(benzyloxy)methyl]oxazolidin-2-one (7b): 70%; cis–trans ratio 30:70; IR 3250, 1750 cm^{-1}. Cis isomer: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.6 (m, 2 H), 3.9–4.4 (m, 1 H), 4.4 (m, 2 H), 4.55 (s, 2 H), 4.65–5.0 (m, 1 H), 6.5 (br s, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) 139.2, 129.4, 128.8, 77.5, 74.4, 69.2, 63.4, 55.0, 20.6. Trans isomer: ^{1}H NMR (CD_3OD) δ 2.05

(s, 3 H), 3.6 (m, 2 H), 3.7–4.1 (m, 1 H), 4.35 (m, 2 H), 4.55 (s, 2 H), 4.4–4.8 (m, 1 H), 4.8 (br s, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) δ 139.2, 129.4, 128.8, 78.0, 74.3, 72.0, 65.4, 55.3, 20.5; MS, *m/e* (relative intensity) 219 ($M^+ - CH_3COOH$, 28), 158 (16), 99 (48), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14. Found: C, 60.18; H, 6.13.

5-(Acetoxymethyl)-4-(hydroxymethyl)oxazolidin-2-one (7c): 67%; cis–trans ratio 7:93; IR 3250, 1745 cm^{-1}. Trans isomer: ^1H NMR (CD_3OD) δ 2.1 (s, 3 H), 3.4–3.85 (m, 3 H), 4.3 (m, 2 H), 4.4–4.8 (m, 1 H), 4.8 (br s, 2 H, OH and NH); ^{13}C NMR (CD_3OD) δ 172.3, 161.2, 77.8, 65.6, 63.8, 57.0, 20.5; MS, *m/e* (relative intensity) 189 (M^+, 3), 148 (30), 98 (24), 97 (25), 72 (100). Anal. Calcd for $C_7H_{11}NO_5$: C, 44.44; H, 5.86. Found: C, 44.41; H, 5.84.

General Procedure for the Preparation of Aminodiol Triacetates (8a,b). A solution of EtOH (5 mL) containing **7a,b** (5 mmol) was added to 4 N KOH (5 mL), and the mixture was refluxed for 24 h. Then 1 N HCl (15 mL) was added, and the solvent was stripped off in vacuo. The residue was then treated with Ac_2O/pyridine for 8 h, and, after removal of the solvent and purification by column chromatography over silica gel with ethyl acetate as eluant, the triacetates **8a,b** were recovered as colorless oils.

3-Acetamido-1,2-diacetoxyhexane (8a): 93%; erythro–threo ratio 55:45; IR 3270, 1745, 1655, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.1–1.7 (m, 4 H), 2.0 (s, 3 H), 2.05 (s, 3 H), 2.1 (s, 3 H), 3.95–4.45 (m, 3 H), 4.85–5.25 (m, 1 H), 6.1 (d, 1 H, NH, *J* = 8 Hz). Erythro isomer: ^{13}C NMR ($CDCl_3$) δ 170.8, 170.7, 170.2, 73.3, 63.2, 48.8, 32.7, 23.2, 20.8, 19.0, 13.8. Threo isomer: ^{13}C NMR ($CDCl_3$) δ 170.8, 170.7, 170.2, 72.6, 63.4, 48.8, 34.3, 23.2, 21.0, 20.8, 19.0, 13.8; MS, *m/e* (relative intensity) 259 (M^+, 2), 214 (13), 156 (21), 139 (42), 114 (100), 72 (63). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16. Found: C, 55.55; H, 8.14.

3-Acetamido-1,2-diacetoxy-4-(benzyloxy)butane (8b): 91%; erythro–threo ratio 30:70; IR 3280, 1745, 1650, 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (br s, 9 H), 3.5 (m, 2 H), 4.2 (m, 2 H), 4.5 (s, 2 H), 4.3–4.7 (m, 1 H), 5.2 (m, 1 H), 6.95 (d, 1 H, NH, *J* = 10 Hz), 7.3 (m, 5 H_{Ar}). Erythro isomer: ^{13}C NMR ($CDCl_3$) δ 170.7, 170.1, 137.7, 128.4, 127.9, 73.2, 70.3, 68.2, 63.0, 48.2, 23.0, 20.8, 20.7. Threo isomer: ^{13}C NMR ($CDCl_3$) δ 170.7, 170.1, 137.7, 128.4, 127.9, 73.5, 70.7, 69.3, 62.9, 48.7, 23.2, 20.8, 20.7; MS, *m/e* (relative intensity) 337 (M^+, 3), 262 (9), 250 (6), 188 (21), 170 (18), 114 (32), 91 (100). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52, H, 6.87. Found: C, 60.49; H, 6.84.

General Procedure for the Preparation of 5-Methyloxazolidin-2-ones (9a–c). Method A. To a solution of **6a–c** (4 mmol) in dry THF (20 mL) under inert atmosphere was added $LiAlH_4$ (8 mmol; 310 mg), and the mixture was stirred for 3 h at room temperature. The reaction was then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. After removal of the solvent and purification by column chromatography over silica gel with cyclohexane–ethyl acetate (6:4) as eluant, 5-methyloxazolidin-2-ones **9a–c** were obtained as colorless oils.

Method B. To a solution of **6a–c** (2 mmol) in ethanol (10 mL) were added Bu_3SnH (4 mmol; 1.16 g) and 2,2′-azobis(2-methylpropanenitrile) (2 mmol; 3.2 g), and the mixture was refluxed for 3 h. After removal of the solvent in vacuo and purification by column chromatography over silica gel with cyclohexane–ethyl acetate (6:4) as eluant, 5-methyloxazolidin-2-ones **9a–c** were obtained as colorless oils.

5-Methyl-4-propyloxazolidin-2-one (9a): method A 70%, method B 85%; cis–trans ratio 55:45; IR 3300, 1740 cm^{-1}. Cis isomer: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.7 (m, 7 H), 3.6–3.9 (m, 1 H), 4.6–5.1 (m, 1 H, *J* = 7.5 Hz), 7.0 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) 77.9, 56.7, 33.1, 20.3, 19.5, 15.0, 14.2. Trans isomer: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2–1.7 (m, 7 H), 3.2–3.55 (m, 1 H), 4.0–4.5 (m, 1 H, *J* = 6 Hz), 7.0 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 80.3, 60.7, 38.2, 20.5, 20.3, 19.5, 14.2; MS, *m/e* (relative intensity) 143 (M^+, 8), 100 (80), 56 (100). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15. Found: C, 58.69; H, 9.14.

4-[(Benzyloxy)methyl]-5-methyloxazolidin-2-one (9b): method A 71%, method B 84%; cis–trans ratio 30:70; IR 3350, 1750 cm^{-1}. Cis isomer: ^1H NMR ($CDCl_3$) δ 1.35 (d, 3 H, *J* = 7 Hz), 3.4–3.9 (m, 3 H), 4.55 (s, 2 H), 4.5–4.9 (m, 1 H, *J* = 7 Hz), 6.0 (m, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) δ 139.2, 129.4, 128.8, 77.3, 74.4, 69.5, 56.4, 15.0. Trans isomer: ^1H NMR ($CDCl_3$) δ 1.4 (d, 3 H, *J* = 7 Hz), 3.4–3.8 (m, 3 H), 4.4–4.8 (m, 1 H, *J* = 5.5 Hz), 4.55 (s, 2 H), 6.1 (m, 1 H, NH), 7.4 (m, 5 H_{Ar}); ^{13}C NMR (CD_3OD) δ 139.2, 129.4, 128.8, 77.6, 74.4, 72.2, 60.2, 20.8, MS, *m/e* (relative intensity) 221 (M^+, 3), 161 (15), 100 (70), 91 (100). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found, C, 65.12; H, 6.81.

4-(Hydroxymethyl)-5-methyloxazolidin-2-one (9c): method A 72%, method B 86%; cis–trans ratio 7:93; IR 3300, 1745 cm^{-1}. Trans isomer: ^1H NMR ($CDCl_3$) δ 1.4 (d, 3 H, *J* = 6 Hz), 3.3–3.8 (m, 3 H), 4.4–4.7 (m, 1 H), 4.8 (br s, 1 H, OH), 7.0 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 77.3, 63.7, 61.9, 20.8; MS, *m/e* (relative intensity) 131 (M^+, 2), 100 (100), 56 (95). Anal. Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92. Found: C, 45.77; H, 6.90.

General Preparation of Amino Alcohols Diacetates (10a,b). A solution of EtOH (5 mL) containing **9a,b** (5 mmol) was added to 4 N KOH (5 mL), and the mixture was refluxed for 24 h. Then 1 N HCl (15 mL) was added, and the solvent was stripped off in vacuo. The residue was then treated with Ac_2O/pyridine for 8 h, and after removal of the solvent and purification by column chromatography over silica gel with ethyl acetate as eluant, diacetates **10a,b** were obtained as colorless oils.

3-Acetamido-2-acetoxyhexane (10a): 94%; erythro–threo ratio 55:45; IR 3300, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.2 (d, 3 H, *J* = 6 Hz), 1.2–1.7 (m, 4 H), 2.0 (s, 3 H), 3.8–4.3 (m, 1 H), 4.6–5.2 (m, 1 H), 6.4 (br s, 1 H, NH). Erythro isomer: ^{13}C NMR (CD_3OD) δ 173.2, 172.2, 73.4, 52.8, 32.6, 22.6, 21.2, 20.2, 15.7, 14.1. Threo isomer: ^{13}C NMR (CD_3OD) δ 173.2, 172.2, 73.1, 53.3, 34.2, 22.6, 21.2, 20.2, 17.2, 14.1; MS, *m/e* (relative intensity) 201 (M^+, 2), 141 (7), 128 (13), 115 (33), 114 (100). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52. Found: C, 59.64; H, 9.51.

2-Acetamido-3-acetoxy-1-(benzyloxy)butane (10b): 93%; erythro–threo ratio 30:70; IR 3300, 1745, 1655, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, *J* = 6 Hz), 2.05 (s, 6 H), 3.4–3.8 (m, 2 H), 4.0–4.4 (m, 1 H), 4.5 (s, 2 H), 4.8–5.3 (m, 1 H), 6.0 (m, 1 H, NH), 7.4 (m, 5 H_{Ar}). Erythro isomer: ^{13}C NMR ($CDCl_3$) δ 170.4, 170.0, 137.7, 128.4, 127.3, 73.3, 70.0, 68.2, 51.7, 23.3, 21.1, 16.9. Threo isomer: ^{13}C NMR ($CDCl_3$) δ 170.4, 170.0, 137.7, 128.4, 127.3, 73.3, 69.7, 69.3, 52.3, 23.3, 21.1, 17.3; MS, *m/e* (relative intensity) 337 (M^+, 3), 277 (6), 204 (15), 160 (100), 114 (65). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87. Found: C, 60.50; H, 6.85.

***N*-(2-Propenyl)-1-methylethanamine Hydrobromide (11).** Allylamine (50 mmol; 2.85 g) and 2-bromopropane (50 mmol; 6.1 g) were refluxed for 24 h, and then the organic phase was stripped off in vacuo. The crude hydrobromide obtained was washed with ether and directly used without further purification: mp 106–108 °C; ^1H NMR (CD_3OD) δ 1.35 (d, 6 H, *J* = 7 Hz), 3.6 (m, 1 H, *J* = 7 Hz), 3.7 (d, 2 H, *J* = 6 Hz), 5.0 (br s, 2 H, NH_2^+), 5.2–6.2 (m, 3 H).

5-(Iodomethyl)-3-isopropyloxazolidin-2-one (12). A suspension of Amberlyst A 26 (24 g; ~3.8 mequiv/g) in the CO_3^{2-} form in a solution of iodine (20 g; 80 mmol) in $CHCl_3$ (100 mL) was stirred for 1 h until the color disappeared. A solution of **11** (5.4 g; 40 mmol) in $CHCl_3$ (40 mL) was then added and the mixture stirred at room temperature for 12 h. The resin was filtered off and the solvent removed under reduced pressure. After chromatography on silica gel with ethyl acetate as eluant, **12** (10.2 g; 95% yield) was obtained as a white solid: mp 76 °C; IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, *J* = 5 Hz), 3.0–3.55 (m, 2 H), 3.25 (d, 2 H, *J* = 3 Hz), 3.7–4.05 (m, 1 H, *J* = 5 Hz), 4.1–4.5 (m, 1 H); MS, *m/e* (relative intensity) 269 (M^+, 20), 254 (100), 210 (50). Anal. Calcd for $C_7H_{12}NO_2I$: C, 31.24; H, 4.49. Found: C, 31.21; H, 4.48.

3-(Acetoxymethyl)-3-isopropyloxazolidin-2-one (13). To a solution of **12** (9.4 g; 35 mmol) in benzene (50 mL) was added Amberlyst A 26 (35 g; ~3.8 mequiv/g) in the AcO^- form and the mixture refluxed for 4 h. The resin was then filtered off and washed with MeOH (60 mL). The solvent was removed in vacuo, and the residue, after purification by chromatography on silica gel with hexane–ethyl acetate (7:3) as eluant, afforded **12** (4.9 g; 70%) as a colorless oil: IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, *J* = 5.5 Hz), 2.1 (s, 3 H), 3.1–3.8 (m, 2 H), 3.9–4.3 (m, 1 H, *J* = 5.5 Hz), 4.25 (d, 2 H, *J* = 3 Hz), 4.45–4.9 (m, 1 H); MS, *m/e* (relative intensity) 201 (M^+, 7), 186 (35), 142 (55), 100 (35), 98 (50), 82 (100). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51. Found: C, 53.70; H, 7.49.

5-(Hydroxymethyl)-3-isopropyloxazolidin-2-one (14). To a solution of **13** (24 mmol; 4.8 g) in ethanol (20 mL) was added anhydrous K_2CO_3 (30 mmol; 4.0 g), and the mixture was stirred

for 12 h at room temperature. After filtration and removal of the solvent in vacuo, the residue was chromatographed on silica gel with ethyl acetate as eluant, to give **14** (3.7 g; 98%) as a colorless oil: IR 3350, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 5.5 Hz), 3.5 (d, 2 H), 3.2–3.8 (m, 2 H), 3.9–4.3 (m, 1 H), 4.5–4.9 (m, 1 H), 4.8 (br s, 1 H, OH); MS, m/e (relative intensity) 159 (M^+, 8), 144 (85), 86 (25), 70 (35), 56 (100). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23. Found: C, 52.79; H, 8.20.

3-Isopropyl-5-[((methylsulfonyl)oxy)methyl]oxazolidin-2-one (15). To a solution of CH_2Cl_2 (30 mL) containing **14** (21 mmol; 3.3 g), Et_3N (30 mmol; 3.0 g), and a catalytic amount of (*N,N*-dimethylamino)pyridine (0.1 g) was added methanesulfonyl chloride (23 mmol; 2.6 g), and the mixture was stirred for 2 h at 0 °C. Then water was added, and the mixture was extracted with CH_2Cl_2 (150 mL). After removal of the solvent, **15** was recovered in a quantitative yield: IR 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 5.5 Hz), 3.1 (s, 3 H), 3.2–3.8 (m, 2 H), 3.9–4.3 (m, 1 H, J = 5.5 Hz), 4.4 (d, 2 H), 4.5–4.9 (m, 1 H). Anal. Calcd for $C_8H_{15}NO_5S$: C, 40.50; H, 6.37. Found: C, 40.47; H, 6.34.

3-Isopropyl-5-[(naphthyloxy)methyl]oxazolidin-2-one (16). To a solution of **15** (20 mmol; 4.7 g) in benzene (35 mL) was added Amberlyst A 26 in the naphtolate form (20 g; ~3.8 mequiv/g), and the suspension was stirred for 24 h at room temperature. The resin was then filtered off, the solvent removed in vacuo, and the residue purified by column chromatography over silica gel with cyclohexane–ethyl acetate (1:1) as eluant, to give **16** (4.0 g; 70%) as a white solid: mp 124 °C; IR 1730, 1590, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, J = 6 Hz), 3.5–4.0 (m, 2 H), 4.1–4.4 (m, 1 H), 4.4 (d, 2 H), 4.5–5.2 (m, 1 H), 6.9–8.4 (m, 7 H_{Ar}); ^{13}C NMR (CD_3COCD_3) δ 127.7, 126.7, 126.2, 125.4, 121.9, 120.9, 105.4, 71.3, 69.1, 44.9, 41.5, 19.2; MS, m/e (relative intensity) 285 (M^+, 88), 226 (20), 144 (90), 100 (100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.54; H, 6.68.

1-(Isopropylamino)-3-[(1-naphthyl)oxy]propan-2-ol (Propranolol) (17). A solution containing **16** (10 mmol; 2.88 g) in ethanol (10 mL) was added to a 4 N KOH solution (10 mL), and the mixture was refluxed for 24 h. The reaction was then extracted with benzene, and the solvent was stripped off in vacuo. The product **17** was obtained in a quantitative yield: mp 93–94 °C (lit.[17] mp 96 °C); IR 3400, 3300, 1590, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (d, 6 H, J = 5.5 Hz), 2.6–3.2 (m, 4 H + OH), 4.0–4.4 (m, 3 H), 6.75–8.4 (m, 7 H_{Ar}); ^{13}C NMR (CD_3OD) δ 128.4, 127.3, 126.9, 126.1, 122.9, 121.4, 105.9, 74.1, 69.8, 51.0, 50.1, 22.7, 22.5; MS, m/e (relative intensity) 259 (M^+, 85), 244 (24), 215 (50), 144 (100). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 74.08; H, 8.14.

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Registry No. **1a**, 2305-21-7; **1b**, 80885-30-9; **1c**, 110-64-5; **3a**, 59874-89-4; **3b**, 93667-62-0; **3c**, 97186-55-5; **4a**, 4181-11-7; **4a**·HCl, 99726-00-8; **4b**, 99726-01-9; **4b**·HCl, 99726-02-0; **4c**, 99726-03-1; **4d**, 99726-04-2; **4e**, 99726-05-3; **5**, 99726-06-4; *cis*-**6a**, 99726-07-5; *trans*-**6a**, 99726-08-6; *cis*-**6b**, 99726-09-7; *trans*-**6b**, 99726-10-0; *cis*-**6c**, 99726-11-1; *trans*-**6c**, 99726-12-2; *cis*-**6d**, 99726-13-3; *trans*-**6d**, 99726-14-4; *cis*-**6e**, 99726-15-5; *trans*-**6e**, 99726-16-6; *cis*-**6f**, 99726-17-7; *trans*-**6f**, 99726-18-8; *cis*-**7a**, 99726-19-9; *trans*-**7a**, 99726-20-2; *cis*-**7b**, 99726-21-3; *trans*-**7b**, 99726-22-4; *cis*-**7c**, 99726-23-5; *trans*-**7c**, 99726-24-6; **8a** (isomer 1), 97186-68-0; **8a** (isomer 2), 99726-25-7; **8b** (isomer 1), 97224-13-0; **8b** (isomer 2), 99726-26-8; *cis*-**9a**, 99726-27-9; *trans*-**9a**, 99726-28-0; *cis*-**9b**, 99726-29-1; *trans*-**9b**, 99726-30-4; *cis*-**9c**, 99726-31-5; *trans*-**9c**, 99726-32-6; **10a** (isomer 1), 99726-33-7; **10a** (isomer 2), 99726-34-8; **10b** (isomer 1), 99726-35-9; **10b** (isomer 2), 99726-36-0; **11**, 99726-37-1; **12**, 99726-38-2; **13**, 95360-67-1; **14**, 83277-30-9; **15**, 99726-39-3; **16**, 70693-88-8; **17**, 13013-17-7; CCl_3CN, 545-06-2; allylamine, 107-11-9; 2-bromopropane, 75-26-3.

(17) Howe, R.; Shanks, R. G. *Nature* (London) **1966**, *210*, 1336.

Thermorubin II: 1,3-Dihydroxy-9*H*-xanthones and 1,3-Dihydroxy-9*H*-xanthenes. New Methods of Synthesis

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Two new efficient methods for the synthesis of 1,3-dihydroxy-9*H*-xanthones have been developed. The first, an adaptation of the classical method of Grover, Shah, and Shah, utilizes Eaton's reagent (P_2O_5/CH_3SO_3H) in place of $ZnCl_2/POCl_3$ to effect the acylation step. The second, an entirely new method, is based on the Friedel–Crafts acylation of a *O,O,O*-tris(trimethylsilyl)phloroglucinol by a 2-chlorobenzoyl chloride. Both methods give good yields. Improvements have been made in the Tanase synthesis of 1,3-dihydroxy-9*H*-xanthenes and the methyl ethers of the latter have been shown to undergo formylation at the 4-position. By contrast, related xanthones are known to undergo substitution at the 2-position. The structures in a series of 2-substituted 9*H*-xanthones including the previously known 2- and 4-methyl-1,3-dihydroxy-9*H*-xanthones have been examined by the use of an NMR shift reagent.

In previous papers[1,2] dealing with the structure of the antibiotic thermorubin, we had cause to synthesize several derivatives of 1,3-dihydroxy-9*H*-xanthone (**1**) amongst which were compounds designated as having structures **2–4**. The regiochemistry of the carboxy group in these substances was assigned solely on the basis of mass spectral data. In view of the fact that these compounds were used[1,2] in structural arguments concerning thermorubin, we decided to seek additional evidence for the position assignment of this group. Our initial intention was to convert the carboxyl to a methyl group and then to compare the product with the known 2- and 4-methyl-1,3-dihydroxyxanthones (**5** and **6**) or their derivatives. However, in our

(1) Moppett, C. E.; Dix, D. T.; Johnson, F.; Coronelli, C. *J. Am. Chem. Soc.* **1972**, *94*, 3269–3272.
(2) Johnson, F.; Chandra, B.; Iden, C. R.; Naiksatam, P.; Kahen, R.; Okaya, Y.; Lin, S.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 5580–5585.

0022-3263/86/1951-0717$01.50/0