138. N,O-Acetals from Pivalaldehyde and Amino Acids for the α-Alkylation with Self-Reproduction of the Center of Chirality. Enolates of 3-Benzoyl-2-(*tert*-butyl)-1,3-oxazolidin-5-ones

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(13.V.85)

The sodium salts of (*S*)-alanine, (*S*)-phenylalanine, (*S*)-valine, and (*S*)-methionine are condensed with pivalaldehyde to imines **5**. Cyclization by treatment with benzoyl chloride in cold CH_2Cl_2 gives mainly (4:1 to > 99:1) the (2*S*,4*S*)-4-alkyl-3-benzoyl-2-(*tert*-butyl)-1,3-oxazolidin-5-ones (**6**; *cis*-configuration) in high yields (85–95%). The oxazolidinones **6** and **7** are deprotonated with lithium diethylamide (LDEA) in tetrahydrofuran (THF) and alkylated (MeI, benzyl bromide) or hydroxyalkylated (benzaldehyde) to 4,4-disubstituted oxazolidinones **9** and **10**, respectively, with high diastereoselectivity (9:1 to 50:1; relative topicity *ul*). Hydrolysis of three of the oxazolidinones to amino acids of known configuration and optical purity indicates that little if any racemization occurs in the process.

In [1] [2], we have shown that amino acids **1** can be α-alkylated[2]) through chiral, non-racemic enolates **3**, derived from 2-(*tert*-butyl)imidazolidinones **2**. Since the *trans*-substituted imidazolidinones **2** are more readily available than the *cis*-isomers, and since the alkylations of the enolates take place preferentially from the face opposite to the bulky *t*-Bu group, the overall transformation **1**→**4** with inversion is accomplished more easily than that with retention [1]. We chose the detour through imidazolidinones, because we could convert only the cyclic amino acids proline [4–6] (special in many ways), hydroxyproline [8], and 'thia-proline' [9] (from cysteine) to oxazolidinones, but not simple amino acids [4].

In the meantime, we found that one of the procedures recommended by *Karady et al.* and *Jung et al.* [10] for the preparation of 2-aryloxazolidinones from amino acids and benzaldehydes can be used also to prepare the corresponding 2-(*tert*-butyl)oxazolidinones (**6**/**7**). Thus, the sodium salts of the amino acids (*S*)-alanine, (*S*)-phenylalanine, (*S*)-valine, and (*S*)-methionine were first condensed with pivalaldehyde to give the *Schiff* bases **5a–d**, respectively. These were cyclized by treatment with benzoyl chloride in CH_2Cl_2 at or below room temperature. By comparison of the NMR spectra with those of the corresponding (*tert*-butyl)imidazolidinones [1] [4], and – in some cases –

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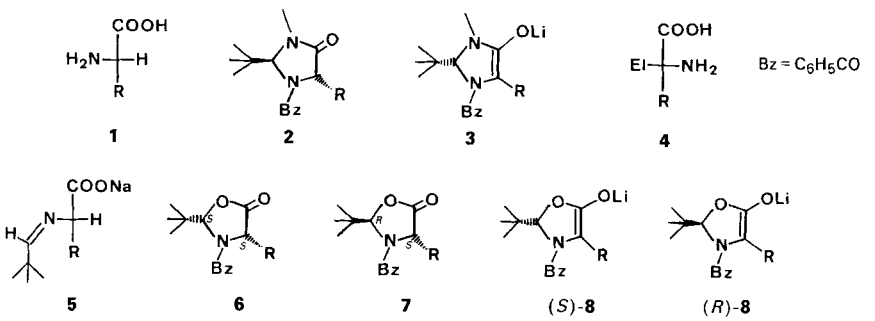
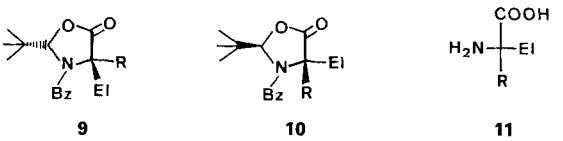
[2]) A conceptually different approach to the synthesis of non-racemic, α-branched α-amino acids, requiring a chiral auxiliary substance, was described by *Schöllkopf* and others, see the review [3] and the discussions in [1] [2] and [4–7].



5, 6, 7	a	b	c	d
R	CH_3	$C_6H_5CH_2$	$(CH_3)_2CH$	$CH_3SCH_2CH_2$



9, 10, 11	a	b	c	d	e	f
R	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	$(CH_3)_2CH$	$(CH_3)_2CH$	$CH_3SCH_2CH_2$
El	$C_6H_5CH_2$	CH_3	$C_6H_5CH(OH)$	CH_3	$C_6H_5CH_2$	CH_3

by measurement of nuclear *Overhauser* effects (NOE), we assign the *cis*-configuration to the major isomers **6** formed under these conditions with preferences above 4:1 (*cf.* [1] [4] [7] [10] [11]). Acidic hydrolysis of the heterocycles (crude product mixtures **6**/**7**) from (*S*)-alanine and from (*S*)-phenylalanine indicates that no racemization had occurred during their preparation – racemization had been a problem which we encountered in some of the cyclizations to the *cis*-disubstituted imidazolidinones [1].

We were surprized to find that treatment of the oxazolidinones **6** and **7** with lithium diisopropylamide (LDA), the most frequently used base for enolate generation, and subsequent addition of electrophiles in THF did not produce reasonable yields of the alkylated products **9** and **10**, respectively. This is in contrast[3]) to the reactivity of the bicyclic oxazolidinones from the prolines and of the imidazolidinones which could easily be alkylated (through enolates **3**) under these conditions [1] [6] [8] [9b]. Screening a number of bases led to lithium diethylamide (LDEA)[4]) as the best one for generation of

[3]) We do not know and did not investigate the reason(s) for the failure of LDA to generate the enolates **8** satisfactorily. One would expect that the oxazolidinones ('lactones') are more acidic than the imidazolidinones ('lactams'). The former should also have a higher reactivity as acylating reagents. The fact that the less hindered base lithium diethylamide (LDEA) is successfully applied shows, however, that nucleophilic attack on the carbonyl group is probably not a complication, see also *Footnote 4*.

[4]) Previously, we used LDEA if steric hindrance in the substrate had to be overcome [12]. Steric hindrance for attack of the base should be larger in the *trans*- (**2** and **7**) than in the *cis*-substituted (**6**) heterocycles. We do not recognize appreciable differences in steric hindrance between analogous imidazolidinones and oxazolidinones. Another base tested with or without dimethyl propylene urea (DMPU) [13] was lithium hexamethyldisilazid (LHMDS) which in one case provided a good yield, with poor diastereoselectivity. We used LHMDS previously to avoid 'self-condensation' of enolates with their precursors [7]. See also *Footnote 3*.

the enolates **8**: the – enantiomeric – products **9** and **10** were obtained in high yields (85–95%) and with satisfactory diastereoisomeric preferences (above 90% ds, before crystallization), similar to those reported by us for the lithium enolates of bicyclic oxazolidinones [6], and by *Karady et al.* for the potassium enolates of 2-aryl-3-(benzyloxycarbonyl)oxazolidinones [10a]. As was demonstrated by the isolation and characterization of (*R*)-α-(methyl)phenylalanine **11a**, hydrolysis of the geminally disubstituted oxazolidinones to free amino acids occurs under much milder conditions than that of analogous imidazolidinones (see **9a**→**11a** and *Procedure I* [14] in the *Exper. Part*).

Thus, a more simple access, comparable reactivity and stereoselectivity, and milder cleavage conditions render the N,O-heterocycles (**6** and **7**) more useful intermediates than the N,N-heterocycles (such as **2**) for overall enantioselective α-alkylation of simple amino acids. The two types of heterocycles are, however, complementary, in as much as they provide the alkylation products of amino acids with inversion (**1**→**4**) and with retention (**1**→**11**), respectively[5]).

In forthcoming papers, we will describe examples of diastereoselective aldol additions and of *Michael* additions to nitroolefins, of heterocyclic enolates such as **3** and **8** (*cf.* product **9**).

We gratefully acknowledge generous supplies of chemicals from the following companies: *BASF AG*, Ludwigshafen (diisopropylamine, pivalaldehyde, THF), *Degussa*, Hanau (amino acids), and *Hoechst AG*, Frankfurt (chlorinated solvents).

Experimental Part

General. All reagents and solvents were purified by the usual methods. DMPU was purified by distillation from CaH_2 under reduced pressure and stored in serum-capped bottles under Ar over molecular sieves 4 Å. THF was distilled under Ar over K. All reactions involving lithium derivatives were carried out under anh. conditions and under Ar [15]. Flash chromatography was performed according to [16]. Bulb-to-bulb distillations were carried out using *Büchi-GRK-50* and reported b.p. are air bath temp. M.p. are uncorrected. IR: *Perkin Elmer 297;* in cm^{-1}. ^{1}H-NMR: *Varian EM 390* (90 MHz); in δ (ppm) rel. to TMS. ^{13}C-NMR: *Varian CFT 20* (20 MHz); in δ (ppm) rel. to TMS.

1. *General Procedure for Preparation of* Schiff-*Base Salts of Amino Acids* **5**. Aq. NaOH (1N; 300 ml, 0.3 mol) was added to the amino acid (0.3 mol). Addition of EtOH (*ca.* 100 ml) and gentle warming was sometimes necessary to effect soln. The soln. was then evaporated under reduced pressure on the rotatory evaporator until precipitation began at which time 1.5 mol-equiv. of pivalaldehyde and 300 ml of pentane or CH_2Cl_2 were added. Azeotropic removal of H_2O (*ca.* 6 ml) in pentane at reflux was completed within 5 to 8 h. The solvent was removed, and the solid was dried under high vacuum overnight. This procedure afforded **5** in quant. yield, ready to use in the following step without further purification.

2. *General Procedures for Preparation of 3-Benzoyl-2-(*tert-*butyl)-1,3-oxazolidin-5-ones* (**6**/**7**). 2.1. *Procedure A.* Benzoyl chloride (14 g, 12 ml, 0.1 mol) was dissolved in 80 ml of CH_2Cl_2 and added in one portion to a stirred suspension of freshly prepared **5** (0.1 mol) in 400 ml of CH_2Cl_2. The suspension, stirred at 0° for 4 h, then at r.t. overnight, slowly became a cloudy soln. The turbid mixture was washed successively with H_2O, 5% $NaHCO_3$, $NaHSO_3$ solns., and H_2O. The dried residue was recrystallized from Et_2O/pentane or hexane to afford **6**/**7**.

2.2. *Procedure B.* Benzoyl chloride (21 g, 17.5 ml, 0.15 mol) was added in one portion to a cooled (−20°) soln. of freshly prepared **5** (0.1 mol) in 150 ml of CH_2Cl_2. The mixture was stirred at −20° for 30 min, then kept at −20° for 1 day and at 0° for 3 to 4 days. Workup as described in *Procedure A* gave **6**/**7** in high yields.

2.3. *Procedure C.* As in *Procedure B*, but benzoyl chloride (0.15 mol) and Et_3N (0.05 mol) were added in one portion. Usual workup yielded **6**/**7**.

2.4. *Procedure D.* As in *Procedure A*, but the suspension was heated at reflux in CH_2Cl_2 (or $CHCl_3$) for 8 to 12 h.

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[5]) For applications on small scales in research laboratories, this is not always an important issue any more, because many D-amino acids are now also commercially available at reasonable prices.

3. *General Procedures for Reactions of the Enolates (S)-***8** *and (R)-***8** *with Various Electrophiles.* 3.1. *Procedure E.* Unless noted otherwise, 0.5M lithium diethylamide (LDEA), 1.2 equiv. in THF/hexane 3:1, was added to a 0.25M soln. of **6** or **7** in THF at −78° (→deep orange). After 40 min, 1.5 equiv. of the electrophile were added, and the temp. was allowed to warm to 20° over 2 h. After stirring overnight at r.t., the resulting light yellow soln. was poured into a cold half-sat NH_4Cl soln. and extracted twice with Et_2O (200 ml). The org. phase was washed with 2 ml of H_2O and dried ($MgSO_4$). The solvent was then removed under reduced pressure.

3.2. *Procedure F.* A 0.5M soln. of LDA (or LHMDS), 1.2 equiv. in THF/hexane 3:1, was added to a 0.25M soln. of **6** or **7** in THF/DMPU (as cosolvent [13]) 4:1 at −78° (→deep brownish red), and then *Procedure E* was followed.

3.3. *Procedure G.* A 0.5M soln. of LDA (or LHMDS), 1.2 equiv. in THF/hexane 3:1, was added to a 0.25M soln. of **6** or **7** in THF at −78° (→deep red). After 30 min, 1.2 equiv. of 1.6M BuLi was added, followed by the electrophile according to *Procedure E.*

4. *General Procedures for Hydrolysis of the Mono- and Dialkylated Oxazolidinones.* 4.1. *Procedure H.* The monoalkylated oxazolidinone **6** or **7** (*ca.* 1 g) was mixed with 20 ml of aq. 6N HCl and heated at reflux for 3 h, after which the heterogeneous mixture was washed twice with 10 ml of CH_2Cl_2. Concentration under reduced pressure gave the crude amino-acid hydrochloride.

4.2. *Procedure I.* The purified dialkylated oxazolidinone **9** or **10** (*ca.* 2 mmol) was mixed with 3 g of $FeCl_3/SiO_2$ (8:100) reagent [14] and 15 ml of aq. 6N HCl and heated at reflux for 3 h. The heterogeneous mixture was filtered, and the filter cake was washed with 10 ml of 6N HCl, and 20 ml of CH_2Cl_2. The aq. layer was separated and washed twice with 10 ml of CH_2Cl_2. Concentration under reduced pressure of the aq. layer gave the crude amino-acid hydrochloride.

5. *General Procedure for Production of the Free Amino Acid.* 5.1. *Procedure J.* The salt was dissolved in 10 ml of H_2O and adsorbed on 30 g of acidic *Lewatit 100S.* The resin was washed with dist. H_2O until neutral, and then the free amino acid was eluted with 1.3N aq. NH_3. The eluant was concentrated *in vacuo.* Complete removal of NH_3 was accomplished by redissolving the substance in H_2O and concentrating in a rotatory evaporator. Finally, drying for 24 h (50°/0.1 Torr) provided pure amino acids.

6. *(2S,4S)- and (2R,4S)-3-Benzoyl-2-(*tert*-butyl)-4-methyl-1,3-oxazolidin-5-one* (**6a** and **7a**). Following *Procedure D,* 53.7 g (0.3 mol) of **5a** and 42 g (0.3 mol, 35 ml) of benzoyl chloride in 1500 ml of CH_2Cl_2 afforded 72 g (92% from (*S*)-alanine) of a 5:1 mixture **6a**/**7a**. Recrystallization from hexane/Et_2O gave 54 g (69%) of **6a** as colorless needles (seeding with a chromatographically obtained sample is necessary). The mother liquor purified by flash chromatography provided 9 g (11.5%) of **7a**. Hydrolysis of the crude mixture in 6N HCl gave, after ion exchange over *Lewatit-H*$^+$ (see *Procedure H* and *J*), (*S*)-alanine of $[\alpha]_D^{25} = +13.26°$ (*c* = 6, 1N HCl) (ee > 95%); the originally employed alanine had $[\alpha]_D^{25} = +14°$.

Data of **6a**. M.p. 94.2–94.5°. $[\alpha]_D^{25} = -29.3°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2966*w*, 1786*s*, 1665*s*, 1600*w*, 1580*w*, 1355*s*, 1275*m*, 1145*m*, 1010*m*, 880*w*. ^{1}H-NMR ($CDCl_3$): 7.45 (*s*, 5 arom. H); 6.13 (*s*, H–C(2)); 4.07 (*q*, *J* = 7, H–C(4)); 1.5 (*d*, *J* = 7, CH_3–C(4)); 1.06 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 174.26 (*s*); 172.82 (*s*); 135.70 (*s*); 130.74 (*d*); 128.64 (*d*); 126.94 (*d*); 95.44 (*d*); 54.18 (*d*); 36.90 (*s*); 25.13 (*q*); 19.55 (*q*). MS: no 261 (M^+), 204 (12, $M^+ - t$-Bu), 106 (8), 105 (100, $C_6H_5CO^+$), 77 (29), 57 (4), 51 (6). Anal. calc. for $C_{15}H_{19}NO_3$ (261.32): C 68.94, H 7.33, N 5.36; found: C 69.14, H 7.55, N 5.35.

Data of **7a**. M.p. 126.8–127.6° (from Et_2O/pentane). $[\alpha]_D^{25} = +79.8°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1790*s*, 1650*s*, 1600*w*, 1580*w*, 1380*s*, 1305*m*, 1154*m*, 1045*m*, 1010*m*, 882*w*. ^{1}H-NMR ($CDCl_3$): 7.75–7.25 (*m*, 5 arom. H); 6.25 (*s*, H–C(2)); 4.37 (*q*, *J* = 7, H–C(4)); 1.11 (*d*, *J* = 7, CH_3–C(4)); 1.04 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 173.45 (*s*); 170.63 (*s*); 136.02 (*s*); 131.75 (*d*); 128.89 (*d*); 127.38 (*d*); 94.38 (*d*); 54.33 (*d*); 39.45 (*s*); 24.51 (*q*); 19.19 (*q*). MS: no 261 (M^+), 204 (12, $M^+ - t$-Bu), 106 (8), 105 (100, $C_6H_5CO^+$), 72 (28), 57 (4, *t*-Bu), 51 (5). Anal. calc. for $C_{15}H_{19}NO_3$ (261.32): C 68.94, H 7.33, N 5.36; found: C 68.99, H 7.36, N 5.37.

Following *Procedure A,* 17.9 g (0.1 mol) of **5a** and 14 g (0.1 mol, 12 ml) of benzoyl chloride in 500 ml of CH_2Cl_2 yielded 24.3 g (93%) of a 2.5:1 mixture **6a**/**7a**.

7. *(2S,4S)-3-Benzoyl-4-benzyl-2-(*t*-butyl)-1,3-oxazolidin-5-one* (**6b**). Following *Procedure B,* 25.5 g (0.1 mol) of **5b** and 21 g (0.15 mol, 17.5 ml) of benzoyl chloride in 150 ml of CH_2Cl_2 gave, after one crystallization (Et_2O/pentane), 31 g (92% from (*S*)-phenylalanine) of practically diastereoisomerically pure **6b** as colorless needles. Hydrolysis of the crude mixture in 6N HCl gave, after ion exchange over *Lewatit-H*$^+$ (see *Procedure H* and *J*) (*S*)-phenylalanine of $[\alpha]_D^{25} = -30.6°$ (*c* = 1, H_2O) (ee 95%); the originally employed (*S*)-phenylalanine had $[\alpha]_D^{25} = -32.2°$.

Data of **6b**. M.p. 137.0–137.6°. $[\alpha]_D^{25} = -29.0°$ (*c* = 1, $CHCl_3$). IR ($CDCl_3$): 2975*m*, 1786*s*, 1665*s*, 1602*w*, 1580*w*, 1358*s*, 1335*m*, 1227*m*, 1196*m*, 1145*m*, 1020*m*. ^{1}H-NMR ($CDCl_3$): 7.44 (*m*, 5 arom. H); 7.15 (*m*, 3 arom. H);

6.75 (*m*, 2 arom. H); 6.07 (*s*, H–C(2)); 4.27 (*t*, *J* = 7, H–C(4)); 3.1 (*d*, *J* = 7, CH_2–C(4)); 1.09 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 173.58 (*s*); 171.33 (*s*); 135.81 (*s*); 130.31 (*d*); 128.97 (*s* and *d*); 128.41 (*d*); 127.00 (*d*); 126.40 (*d*); 95.17 (*d*); 59.19 (*d*); 40.80 (*t*); 36.97 (*s*); 25.28 (*q*). MS: 281 (8), 280 (41, $M^+ - t$-Bu), 106 (27), 105 (100, $C_6H_5CO^+$), 91 (13), 78 (5), 77 (55), 57 (7), 51 (7), 41 (6). Anal. calc. for $C_{21}H_{23}NO_3$ (337.42): C 74.75, H 6.87, N 4.15; found: C 74.78, H 6.96, N 4.01.

Following *Procedure D*, 25.5 g (0.1 mol) of **5b** and 17 g (0.12 mol, *ca.* 14 ml) of benzoyl chloride in 500 ml of $CHCl_3$ yielded 20.2 g (60% from (*S*)-phenylalanine) of **6b**. Hydrolysis of the crude mixture in 6N HCl gave, after ion exchange over *Lewatit-H*$^+$ (see *Procedure H* and *J*), (*S*)-phenylalanine of $[\alpha]_D^{25} = -24.2°$ (*c* = 1, H_2O) (ee > 75%); thus, partial racemization had occurred during cyclization under reflux.

8. *(2S,4S) and (2R,4S)-3-Benzoyl-2-(*tert*-butyl)-4-isopropyl-1,3-oxazolidin-5-one* (**6c** and **7c**). Following *Procedure B*, 20.7 g (0.1 mol) of **5c** and 21 g (0.15 mol, 17.5 ml) of benzoyl chloride in 150 ml of CH_2Cl_2 afforded 27.2 g (94% from (*S*)-valine) of a 4:1 mixture of **6c**/**7c**. Recrystallization from Et_2O gave 5 g (17.3%) of **7c**. The mother liquid, after flash chromatography and recrystallization from hexane, provided 19.5 g (67.5%) of **6c** as a colorless powder.

Data of **6c**. M.p. 60.5–61.0°. $[\alpha]_D^{25} = +23.8°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1780*s*, 1655*s*, 1600*w*, 1580*w*, 1356*w*, 1330*m*, 1242*w*, 1195*m*, 1170*w*, 1145*w*, 1020*m*, 838*w*. ^{1}H-NMR ($CDCl_3$): 7.7–7.1 (*m*, 5 arom. H); 5.95 (*s*, H–C(2)); 4.29 (*d*, *J* = 10, H–C(4)); 2.3–1.7 (*m*, CH–C(4)); 1.14 (*d*, *J* = 7, CH_3–CH–C(4)); 0.93 (*s*, $(CH_3)_3C$); 0.86 (*d*, *J* = 7, CH_3–CH–C(4)). ^{13}C-NMR ($CDCl_3$): 173.04 (*s*); 171.73 (*s*); 135.99 (*s*); 129.69 (*d*); 128.51 (*d*); 126.47 (*d*); 95.94 (*d*); 61.91 (*d*); 36.78 (*s*); 31.94 (*d*); 25.35 (*q*); 19.82 (*q*); 19.69 (*q*). MS: 274 (0.6, $M^+ - CH_3$), 232 (41, $M^+ - t$-Bu), 122 (7), 106 (36), 105 (100, $C_6H_5CO^+$), 77 (85), 57 (102), 51 (15), 41 (12). Anal. calc. for $C_{17}H_{23}NO_3$ (289.37): C 70.56, H 8.01, N 4.84; found: C 70.28, H 7.82, N 4.80.

Data of **7c**. M.p. 180.2–180.6°. $[\alpha]^{25} = +79.6°$ (*c* = 1, $CHCl_3$). IR ($CDCl_3$): 2970*m*, 1786*s*, 1650*s*, 1600*w*, 1580*w*, 1375*s*, 1230*s*, 1200*m*, 1150*m*, 1055*m*. ^{1}H-NMR ($CDCl_3$): 7.9–7.3 (*m*, centred at 7.5, 5 arom. H); 6.14 (*s*, H–C(2)); 4.29 (*d*, *J* = 3.75, H–C(4)); 2.14 (*m*, CH–C(4)); 1.01 (*s*, $(CH_3)_3C$); 0.92 (*d*, *J* = 7, CH_3); 0.77 (*d*, *J* = 7, CH_3). ^{13}C-NMR ($CDCl_3$): 171.07 (*s*); 136.18 (*s*); 132.10 (*d*); 129.13 (*d*); 127.19 (*d*); 94.71 (*d*); 63.62 (*d*); 40.03 (*s*); 30.6 (*d*); 24.84 (*q*); 17.72 (*q*); 15.00 (*q*). MS: 274 (1.8, $M^+ - 15$), 270 (2), 233 (7), 232 (46, $M^+ - t$-Bu), 106 (27), 105 (100, $C_6H_5CO^+$), 78 (5), 77 (59), 57 (9), 55 (5), 51 (8), 41 (9). Anal. calc. for $C_{17}H_{23}NO_3$ (289.37): C 70.56, H 8.01, N 4.84; found: C 70.40, H 7.89, N 4.74.

Following *Procedure A*, 20.7 g (0.1 mol) of **5c** and 17 g (0.12 mol, *ca.* 14 ml) of benzoyl chloride in 500 ml of CH_2Cl_2 gave 26.6 g (92% overall yield from (*S*)-valine) of a 2:1 mixture **6c**/**7c**.

9. *(2S,4S)-3-Benzoyl-2-(*tert*-butyl)-4-(3'-thiabutyl)-1,3-oxazolidin-5-one* (**6d**). Following *Procedure B*, 23.9 g (0.1 mol) of **5d** and 21 g (0.15 mol, 17.5 ml) of benzoyl chloride in 150 ml of CH_2Cl_2 afforded 30.5 g (95% from (*S*)-methionine) of a 5:1 mixture **6d**/**7d**. Recrystallization from MeOH (or from Et_2O/pentane/CH_2Cl_2) gave 22.5 g (70%) of pure, colorless **6d**. M.p. 126.2–126.6°. $[\alpha]_D^{25} = +62.2°$ (*c* = 1, $CHCl_3$). IR ($CDCl_3$): 2970*m*, 1785*s*, 1675*s*, 1600*w*, 1360*m*, 1230*w*, 1200*m*, 850*s*, 750*s*, 650*s*. ^{1}H-NMR ($CDCl_3$): 7.46 (*m*, sharp, 5 arom. H); 6.10 (*s*, H–C(2)); 4.20 (*m*, H–C(4)); 2.8–1.9 (*m*, 2 CH_2); 1.87 (*s*, CH_3S); 1.04 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 173.56 (*s*); 171.87 (*s*); 135.71 (*s*); 130.46 (*d*); 128.84 (*d*); 126.45 (*d*); 95.39 (*d*); 56.38 (*d*); 36.95 (*s*); 34.04 (*t*); 30.27 (*t*); 25.13 (*q*); 15.23 (*q*). MS: 321 (2.1, M^+), 264 (0.4, $M^+ - t$-Bu), 236 (4), 216 (7), 199 (13), 171 (10), 156 (3), 114 (5), 106 (8), 105 (100, $C_6H_5CO^+$), 102 (2), 77 (28), 61 (8), 51 (4), 41 (4). Anal. calc. for $C_{17}H_{23}NO_3S$ (321.44): C 63.52, H 7.21, N 4.36, S 9.98; found: C 63.51, H 7.15, N 4.34, S 9.98.

Data of **7d**. From the ^{1}H-NMR of crude **6d**/**7d**: 7.8–7.3 (*m*, 5 arom. H); 6.21 (*s*, H–C(2)); 4.52 (*m*, H–C(4)); 2.45–1.4 (*m*, 2 CH_2); 1.83 (*s*, CH_3S); 1.02 (*s*, $(CH_3)_3C$).

Following *Procedure C*, 23.9 g (0.1 mol) of **5d**, 21 g (0.15 mol, 17.5 ml) of benzoyl chloride and 5.05 g (0.05 mol, *ca.* 7 ml) of Et_3N in 150 ml of CH_2Cl_2 gave 24 g (75% from (*S*)-methionine) of a 4:1 mixture **6d**/**7d**.

10. *(2S,4R)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-4-methyl-1,3-oxazolidin-5-one* (**9a**). Following *Procedure E*, 1.31 g (5 mmol) of **6a** and 1.25 ml (10 mmol) of benzyl bromide provided, after recrystallization from Et_2O/pentane, 1.63 g (93%) of **9a** as colorless crystals (ds > 98%, from the ^{13}C-NMR of the crude product). M.p. 123.5–124.0°. $[\alpha]_D^{25} = -112.4°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1786*s*, 1640*s*, 1600*w*, 1578*w*, 1380*s*, 1175*m*, 876*m*, 700*w*. ^{1}H-NMR ($CDCl_3$): 7.8–6.5 (*m*, centred at 7.25, 10 arom. H); 5.5 (br. *s*, H–C(2)); 3.48 (*AB*, *J* = 14, $C_6H_5CH_2$); 1.94 (br. *s*, CH_3–C(4)); 0.7 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 175.21 (*s*); 17.00 (br. *s*); 136.29 (*s*); 134.87 (*s*); 130.69 (*d*); 130.02 (*d*); 128.57 (*d*); 128.02 (*d*); 127.32 (*d*); 95.00 (*d*); 65.50 (*s*); 42.75 (br. *t*); 38.41 (*s*); 25.23 (2*q*). MS: 336 (1.5, $M^+ - 15$), 294 (23, $M^+ - t$-Bu), 205 (7), 149 (100), 125 (13), 123 (15), 111 (24), 105 (40), 97 (38), 95 (28), 85 (36), 83 (43), 81 (30), 71 (58), 69 (60), 57 (97, *t*-Bu), 55 (61), 43 (71), 41 (45). Anal. calc. for $C_{22}H_{25}NO_3$ (351.44): C 75.19, H 7.17, N 3.99; found: C 75.31, H 7.19, N 3.97.

11. *(2S,4S)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-4-methyl-1,3-oxazolidin-5-one* (**9b**). Following *Procedure E*, 1.69 g (5 mmol) of **6b** and 1.25 ml (20 mmol) of MeI yielded, after flash chromatography (Et_2O/pentane 1:6), 1.55 g (88%) of **9b** as colorless viscous oil (ds > 98%, by ^{13}C-NMR of the crude product). $[\alpha]_D = -1.3°$ and $[\alpha]_{365} = +11.9°$ (*c* = 1, $CHCl_3$). IR ($CDCl_3$): 2970*m*, 1782*s*, 1645*s*, 1600*w*, 1578*w*, 1444*m*, 1355*s*, 1330*s*, 1215*m*, 1185*s*, 1050*m*, 1015*m*. ^{1}H-NMR ($CDCl_3$): 7.52 (br. *s*, 5 arom. H); 7.35–6.90 (*m*, 5 arom. H); 6.12 (*s*, H–C(2)); 3.36 (*s*, CH_2–C(4)); 1.35 (*s*, CH_3–C(4)); 0.85 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 173.91 (*s*); 173.84 (*s*); 137.23 (*s*); 135.21 (*s*); 131.07 (*d*); 130.76 (*d*); 128.43 (*d*); 127.98 (*d*); 127.88 (*d*); 127.12 (*d*); 94.00 (*d*); 63.38 (*s*); 44.78 (*t*); 31.71 (*s*); 25.20 (*q*); 25.06 (*q*). MS: 336 (0.8, $M^+ - 15$), (13, $M^+ - t$-Bu), 260 (22), 117 (5), 106 (43), 105 (100, $C_6H_5CO^+$), 91 (25), 77 (87), 57 (21), 51 (11), 41 (17). Anal. calc. for $C_{22}H_{25}NO_3$ (351.44): C 75.19, H 7.17, N 3.99; found: C 75.12, H 6.98, N 3.92.

Following *Procedure F*, 1.69 g (5 mmol) of **6b** and 1.25 ml (20 mmol) of MeI in THF/DMPU [13] gave 1.19 g (68%) of **9b** (ds 92%) and 505 mg (30%) of **6b**.

Following *Procedure G*, 1.69 g (5 mmol) of **6b** and 1.25 ml (20 mmol) of MeI yielded 890 mg (51%) of a 7:3 mixture **9b**/**9a**.

12. *(2S,4R)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-4-(α-hydroxybenzyl)-1,3-oxazolidin-5-one* (**9c**). Following *Procedure E*, 1.69 g (5 mmol) of **6b** and 795 mg (765 µl, 7.5 mmol) of benzaldehyde were employed. The reaction was quenched 2–5 min after adding benzaldehyde at −78°, with a soln. of 900 mg (15 mmol) of glacial AcOH in 5 ml of Et_2O. The mixture was extracted twice with Et_2O (200 ml). Then, the org. phase was washed successively with sat. $NaHCO_3$ and sat. NaCl soln., dried ($MgSO_4$), and concentrated under reduced pressure to give, after one crystallization, 2.13 g (96%) of **9c** as a white powder (ds > 95%). M.p. 141.9–142.2°. $[\alpha]_D = -85.8°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 3520*w*, 3330*m*, 2960*m*, 1768*s*, 1722*s*, 1600*w*, 1582*w*, 1265*s*, 1105*m*, 1092*m*, 1070*m*, 1025*m*. ^{1}H-NMR ($CDCl_3$): 8.3–7.8 (*m*, 2 arom. H); 7.8–6.9 (*m*, 13 arom. H); 6.12 (*s*, H–C(2)); 4.42 (*d*, *J* = 11, C_6H_5–C*H*(OH)); 3.11 (*AB*, *J* = 14, $C_6H_5CH_2$); 2.39 (*d*, *J* = 11, OH); 0.52 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 176.36 (*s*); 165.06 (*s*) [arom. C: 135.95 (*s*); 134.07 (*s*); 133.23 (*d*); 130.53 (*d*); 129.94 (*s*); 129.79 (*s*); 129.23 (*d*); 128.98 (*d*); 128.62 (*d*); 128.52 (*d*); 128.26 (*d*); 127.89 (*d*)]; 98.87 (*d*); 80.10 (*d*); 69.41 (*s*); 39.33 (*t*); 33.14 (*s*); 23.81 (*q*). MS: 352 (0.5, $M^+ - 91$), 337 (1), 278 (19), 277 (83), 262 (7), 234 (12), 220 (40), 193 (30), 186 (17), 178 (19), 165 (7), 145 (13), 142 (22), 122 (40), 117 (14), 116 (47), 115 (69), 105 (54, $C_6H_5CO^+$), 91 (100, $C_7H_7^+$), 77 (41), 69 (17), 57 (11), 51 (16), 44 (22), 41 (14). Anal. calc. for $C_{28}H_{29}NO_4$ (443.54): C 75.82, H 6.59, N 3.16; found: C 75.56, H 6.64, N 3.10.

13. *(2S,4S)-3-Benzoyl-2-(*tert*-butyl)-4-isopropyl-4-methyl-1,3-oxazolidin-5-one* (**9d**). Following *Procedure E*, 1.16 g (4 mmol) of **6c** and 1.00 ml (16 mmol) of MeI provided, after flash chromatography (Et_2O/pentane 1:7), 290 mg (25%) of **6c** and 645 mg (53%) of diastereoisomerically pure **9d** as a colorless viscous oil. $[\alpha]_D = +38.9°$ (*c* = 1, $CHCl_3$). IR ($CDCl_3$): 2975*m*, 1775*s*, 1655*s*, 1600*w*, 1580*w*, 1445*w*, 1352*m*, 1330*m*, 1300*s*, 1245*m*, 1186*s*, 1170*s*, 1150*m*, 1130*m*, 1016*m*, 820*w*. ^{1}H-NMR ($CDCl_3$): 7.8–7.3 (*m*, centred at 7.48, 5 arom. H); 5.98 (*s*, H–C(2)); 2.20–1.65 (*m*, CH–C(4)); 1.45 (*s*, CH_3–C(4)); 1.20 (*d*, *J* = 7, CH_3–CH–C(4)); 1.09 (*d*, *J* = 7, CH_3–CH–C(4)); 1.02 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 176.94 (*s*); 173.61 (*s*); 137.26 (*s*); 131.48 (*d*); 128.31 (*d*); 128.00 (*d*); 93.69 (*d*); 67.71 (*s*); 37.86 (*s*); 35.45 (*d*); 26.01 (*q*); 22.55 (*q*); 18.60 (*q*); 17.47 (*q*). MS: 246 (11, $M^+ - t$-Bu), 154 (3), 106 (16), 105 (100, $C_6H_5CO^+$), 77 (40), 69 (7), 57 (12, *t*-Bu), 55 (8), 51 (7), 43 (8), 41 (16). Anal. calc. for $C_{18}H_{25}NO_3$ (303.40): C 71.26, H 8.31, N 4.62; found: C 71.03, H 8.48, N 4.88.

14. *(2R,4R)-3-Benzoyl-2-(*tert*-butyl)-4-isopropyl-4-methyl-1,3-oxazolidin-5-one* (**10d**). Following *Procedure G*, 870 mg (3 mmol) of **7c**, with LHMDS, and 0.75 ml (12 mmol) of MeI yielded 730 g (80%) of a mixture of **10d** (ds > 66%) and its (2*R*,4*S*)-isomer. Flash chromatography (Et_2O/pentane 1:7) and a bulb-to-bulb distillation (180°, 0.5 Torr)[6] provided 400 mg (44%) of diastereoisomerically pure **10d** as a colorless visous oil (ds > 95%). $[\alpha]_D = -36.0°$ (*c* = 0.5, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 2890*w*, 1780*s*, 1656*s*, 1600*w*, 1580*w*, 1448*m*, 1380*m*, 1355*m*, 1300*m*, 1172*s*, 1150*w*, 1028*m*, 920*w*, 700*w*. ^{1}H-NMR ($CDCl_3$): 7.70–7.15 (*m*, centred at 7.47, 5 arom. H); 5.95 (*s*, H–C(2)); 1.93 (*sept.*, CH–C(4)); 1.44 (*s*, CH_3–C(4)); 1.19 (*d*, *J* = 7, CH_3–CH–C(4)); 1.08 (*d*, *J* = 7, CH_3–CH–C(4)); 1.02 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 176.97 (*s*); 173.66 (*s*); 137.33 (*s*); 131.51 (*d*); 128.35 (*d*); 128.03 (*d*); 93.74 (*d*); 67.76 (*s*); 37.88 (*s*); 35.49 (*d*); 26.05 (*q*); 22.59 (*q*); 18.64 (*q*); 17.51 (*q*). MS: 246 (4, $M^+ - t$-Bu), 228 (3), 159 (6), 153 (9), 149 (19), 124 (5), 106 (9), 105 (100, $C_6H_5CO^+$), 91 (8), 87 (10), 77 (28), 71 (19), 70 (13), 69 (29), 57 (44), 56 (14), 55 (23), 43 (49), 42 (18), 41 (44). Anal. calc. for $C_{18}H_{25}NO_3$ (303.40): C 71.26, H 8.31, N 4.62; found: C 71.51, H 8.09, N 4.76.

Data of the Minor (2R,4S)-Isomer. From the ^{1}H-NMR of the crude mixture: 7.7–7.15 (*m*, 5 arom. H); 5.5 (br. *s*, H–C(2)); 2.4–1.6 (*m*, H–C(4)); 1.39 (*s*, CH_3S); 1.25 (*d*, *J* = 7, CH_3); 1.17 (*d*, *J* = 7, CH_3); 1.00 (*s*, $(CH_3)_3C$).

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[6]) Slight decomposition may occur during distillation.

Following *Procedure E*, 870 mg (3 mmol) of **7c** and 0.75 ml (12 mmol) of MeI provided 680 mg (75%) of a mixture of **10d** (ds > 85%) and its (2*R*,4*S*)-isomer. It was interesting to note that the alkylation of **7c** following *Procedure E*, with LDA or LHMDS and MeI, provided only 10% of **10d** and 90% of **7c**.

15. *(2R,4R)-3-Benzoyl-4-benzyl-2-(*tert*-butyl)-4-isopropyl-1,3-oxazolidin-5-one* (**10e**). Following *Procedure F*, 1.16 g (4 mmol) of **7c**, with LHMDS, and 1.00 ml (8 mmol) of benzyl bromide in THF/DMPU [13] gave, after flash chromatography, 700 mg (40%) of white solid **10e** (ds > 93%). For anal. purposes, **10e** was crystallized from hexane: colorless crystals of m.p.: 130.2–131.0°. $[\alpha]^{25} = +13.5°$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1780*s*, 1650*s*, 1600*w*, 1580*w*, 1482*w*, 1360*s*, 1175*s*, 1085*m*, 1060*m*, 1030*m*, 904*w*, 872*w*. ^{1}H-NMR ($CDCl_3$): 7.5–7.0 (*m*, centred at 7.20, 8 arom. H); 6.70–6.40 (*m*, 2 arom. H); 5.40 (*s*, H–C(2)); 3.56 (*AB*, $J = 14$, CH_2–C(4)); 2.46 (*sept.*, $J = 7$, CH–C(4)); 1.38 (*d*, $J = 7$, CH_3–CH–C(4)); 1.34 (*d*, $J = 7$, CH_3–CH–C(4)); 0.67 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 174.62 (*s*); 171.07 (*s*); [arom. C: 136.92 (*s*); 135.57 (*s*); 130.88 (*d*); 130.01 (*d*); 128.67 (*d*); 127.94 (*d*); 127.71 (*d*); 127.13 (*d*)]; 95.19 (*d*); 71.95 (*s*); 37.92 (*s*); 37.16 (*t*); 35.38 (*d*); 25.91 (*q*); 19.99 (*q*); 18.88 (*q*). MS: 322 (2, $M^+ - t$-Bu), 106 (8), 105 (100, $C_6H_5CO^+$), 91 (13), 78 (2), 77 (22), 57 (4), 51 (3), 43 (3), 41 (4). Anal. calc. for $C_{24}H_{29}NO_3$ (379.50): C 75.96, H 7.70, N 3.69; found: C 75.91, H 7.60, N 3.63.

Following *Procedure G*, 870 mg (3 mmol) of **7c** and 0.75 ml (6 mmol) of benzyl bromide in THF provided 110 mg (< 10%) of **10e**.

16. *(2S,4S)-3-Benzoyl-2-(*tert*-butyl)-4-methyl-4-(3'-thiabutyl)-1,3-oxazolidin-5-one* (**9f**). Following *Procedure E*, 1.61 g (5 mmol) of **6d** and 1.25 ml (20 mmol) of MeI yielded 1.62 g (91%) of crude solid **9f** (ds > 95%). Flash chromatography provided 1.23 g (69%) of pure **9f** as white crystals and 140 mg (9%) of **6d**.

Data of **9f**. M.p. 102.5–103.0°. $[\alpha]_D = +10.8°$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): 2975*m*, 1785*s*, 1655*s*, 1600*w*, 1580*w*, 1355*m*, 1300*m*, 1180*m*, 1145*m*, 1050*m*, 1016*w*, 926*w*, 665*m*. ^{1}H-NMR ($CDCl_3$): 7.50 (*s*, 5 arom. H); 6.13 (*s*, H–C(2)); 3.10–1.80 (*m*, 2 CH_2); 2.04 (*s*, CH_3S); 1.36 (*s*, CH_3–C(4)); 1.00 (*s*, $(CH_3)_3C$). ^{13}C-NMR ($CDCl_3$): 175.10 (*s*); 174.15 (*s*); 136.86 (*s*); 131.53 (*d*); 128.45 (*d*); 127.92 (*d*); 94.13 (*d*); 63.01 (*s*); 39.35 (*t*); 37.88 (*s*); 28.86 (*t*); 25.43 (*q*); 24.88 (*q*); 15.32 (*q*). MS: 335 (0.3, M^+); 278 (2.3, $M^+ - t$-Bu), 250 (8), 222 (2), 174 (2), 106 (8), 105 (100, $C_6H_5CO^+$), 77 (25), 75 (3), 61 (5), 57 (4), 42 (4), 41 (6). Anal. calc. for $C_{18}H_{25}NO_3S$ (335.46): C 64.45, H 7.51, N 4.18, S 9.56; found: C 64.71, H 7.53, N 4.29, S 9.64.

17. *(2R)-2-Amino-2-methyl-3-phenylpropanoic Acid (= (R)-α-(methyl)phenylalanine;* **11a**). Following *Procedure I*, 705 mg (2 mmol) of **9a** in 15 ml of aq. 6N HCl in presence of 3 g of $FeCl_3/SiO_2$ (8:100) reagent [14] provided crude **11a**·HCl[7]) Cation-exchange chromatography by *Procedure J* gave 340 (95%) of **11a** as colorless crystals. M.p. 308–310°. $[\alpha]^{24}_{578} = +20.0°$ ($c = 0.1$, MeOH) ([10] [17]: m.p. 307–310° (dec.), $[\alpha]_{578} = +20.0°$ ($c = 0.1$, MeOH), $[\alpha]^{25}_{578} = -22.8°$ ($c = 1$, H_2O)). ^{1}H-NMR (D_2O, HDO = 4.8 ppm): 7.4 (*m*, 5H); 3.01 (*AB*, $J = 14$, CH_2–C(2)); 1.41 (br. *s*, CH_3). MS: 180 (1.3, $M^+ + 1$), 179 (1, M^+), 165 (3), 135 (3), 91 (17), 88 (9), 84 (34), 72 (9), 71 (8), 70 (11), 69 (13), 57 (28), 55 (23), 44 (100), 43 (27), 42 (22), 41 (40), 39 (16), 29 (17), 28 (30).

REFERENCES

[1] R. Naef, D. Seebach, *Helv. Chim. Acta* **1985,** *68,* 135; D. Seebach, J. D. Aebi, R. Naef, Th. Weber, *Helv. Chim. Acta* **1985,** *68,* 144.

[2] D. Seebach, in 'The Robert A. Welch Foundation Conferences on Chemical Research. XXVII. Stereospecificity in Chemistry and Biochemistry', Houston, Texas, Nov. 7–9, 1983, published in the proceedings of the above conference, Welch Foundation, Houston, 1984, pp. 93–145.

[3] U. Schöllkopf, *Pure Appl. Chem.* **1983,** *55,* 1799; U. Schöllkopf, *Topics Curr. Chem.* **1983,** *109,* 65.

[4] R. Naef, Dissertation No. 7442, ETH Zürich, 1983.

[5] D. Seebach, R. Naef, *Helv. Chim. Acta* **1981,** *64,* 2704.

[6] D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983,** *105,* 5390.

[7] D. Seebach, R. Naef, G. Calderari, *Tetrahedron* **1984,** *40,* 1313.

[8] Th. Weber, D. Seebach, *Helv. Chim. Acta* **1985,** *68,* 155.

[9] a) D. Seebach, Th. Weber, *Tetrahedron Lett.* **1983,** *24,* 3316; b) D. Seebach, Th. Weber, *Helv. Chim. Acta* **1984,** *67,* 1650.

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[7]) Hydrolysis with 6N HCl gave, after 30 h at reflux, only 30% of crude **11a**·HCl. It is interesting to note that the hydrolysis following *Procedure I* at r.t. provided 90% of conversion over 1 day.

[10] S. Karady, J.S. Amato, L.M. Weinstock, *Tetrahedron Lett.* **1984,** *25,* 4337; *cf.* also R.G. Hiskey, J.M. Jung, *J. Am. Chem. Soc.* **1963,** *85,* 578.
[11] T. Poloński, *Tetrahedron* **1983,** *39,* 3139.
[12] D. Seebach, D. Wasmuth, *Angew. Chem.* **1981,** *93,* 1007; *ibid. Int. Ed.* **1981,** *20,* 971.
[13] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982,** *65,* 385.
[14] A. Fadel, J. Salaün, *Tetrahedron* **1985,** *41,* 413; *ibid.* **1985,** *41,* 1267.
[15] D. Seebach, T. Weller, G. Protschuk, A.K. Beck, M.S. Hoekstra, *Helv. Chim. Acta* **1981,** *64,* 716.
[16] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.
[17] F.W. Bollinger, *J. Med. Chem.* **1971,** *14,* 373.