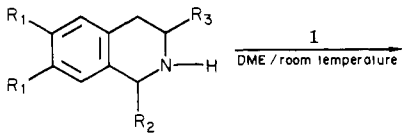
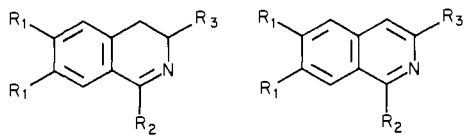


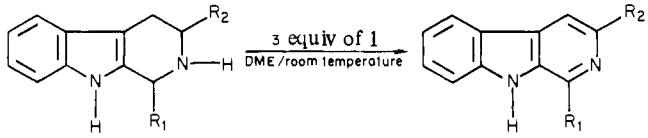
2



3 4

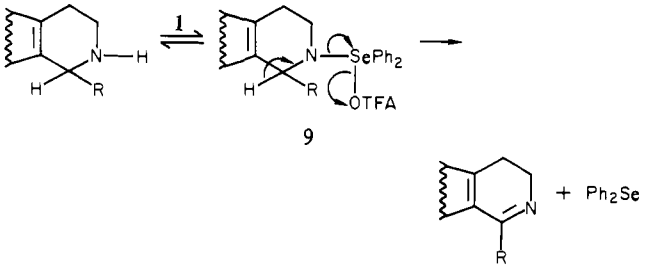
2	1, equiv	yield, % 3	4
a, R_1 = MeO; R_2 = R_3 = H	2	80	0
b, R_1 = MeO; R_2 = Me; R_3 = H	3	81	10
c, R_1 = MeO; R_3 = H; R_2 = 3,4-$(MeO)_2C_6H_3CH_2$	6	85 (R_2 = ArCO)	10
d, R_1 = MeO; R_2 = COOH; R_3 = H	2	100	
e, R_1 = R_2 = H; R_3 = COOH	3	0	R_1 = R_2 = H; R_3 = CO_2Me, 40 + R_1 = R_2 = R_3 = H, 26%
f, R_1 = R_2 = H; R_3 = CO_2Me	3	0	100

the second oxidation step from the dihydro intermediate.



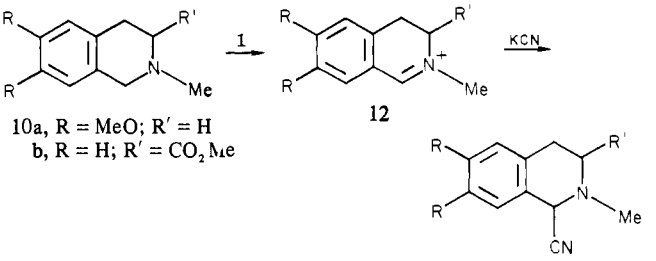
5, R_1 = R_2 = H — 7, 61%
6, R_1 = Me; R_2 = CO_2Me — 8, 70%

The mechanism for the initial oxidation of the tetrahydropyridine system to its 3,4-dihydro derivative is presumed to involve an aminoselenurane intermediate **9**. The formation of **9** would be expected to occur via the displacement[22] of a trifluoroacetate ligand from reagent **1**. The loss of a benzylic proton from **9** completes the oxidation process to an imine and diphenyl selenide. The reluctance of products **3a–d** to undergo clean oxidation to their isoquinolines reflects the lack of driving force for an 1,2-iminoselenurane to lose a C-4 proton. The facile oxidation of **2f** to its isoquinoline **4f** is thought to proceed via its 1,4-dihydroisoquinoline, which in turn forms a 2,3-iminium selenurane.



9

Having established that secondary amines are readily oxidized by the electrophilic selenurane **1**, we next examined the fate of tertiary amines with reagent **1**. Since the expected oxidation products of the *N*-methyl-1,2,3,4-tetrahydroisoquinolines **10a** and **10b**[23] were the 1,2-iminium species **12**, which are usually difficult to isolate, their reaction mixtures were quenched with an aqueous solution of potassium cyanide. The oxidations of **10a** and **10b** with 3 equiv of selenurane **1** at room temperature proceeded regiospecifically to the 1-cyanotetrahydroisoquinolines **11a**[24] and **11b** in high yields. This overall transformation is an oxidative analogue of the Reissert reaction. Evidently, there was no effect of the carbomethoxy group of **10b** on the regioselectivity of the iminium ion formation. These oxidations are envisaged to involve an ammonium selenurane.



10a, R = MeO; R′ = H
b, R = H; R′ = CO_2Me

12

11a, 90%
b, 78%

In summary, the oxidations of secondary and tertiary amines by diphenylselenium bis(trifluoroacetate) (**1**) represent a very mild, two-electron process that mimics a number of biological oxidations of amines. We feel that the use of hypervalent selenuranes as oxidants promises to offer more selective and efficient oxidations of heterocarbon functionality. Further work is in progress to explore the synthetic potential of this new class of reagents as well as the mechanism of oxidation.

Acknowledgment. R.D.L. is grateful for a Dow–Britton Fellowship and Chemistry Department Fellowships (Moses Gomberg and Robert Ruthruff) during the course of this work. We also thank Dr. Alan Schwartz for the initial characterization of the selenurane **1**.

(22) The S_N1-like ionization of certain sulfuranes has been postulated for the oxidations of nitrogen compounds: Martin, J. C.; Balthazor, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 152.

(23) **10a**: reference for **2a**. Data for **10b**: **10b**·HCl, mp 192–193 °C; ^{1}H NMR (60 MHz, $CDCl_3$) (Me_4Si) δ 2.5 (s, 3 H), 3.0 (m, 2 H), 3.5 (m, 1 H), 3.6 (s, 3 H), 3.7 (m, 2 H, buried), 7.0 (s, 4 H); MS *m/e* 205 (M^+), 146 (M − 59). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.34; H, 7.38; N, 6.75.

(24) **11a**: Eckhardt, E. *Magy. Kem. Foly.* **1974**, *70*, 295. *Chem. Abstr.* **1974**, *61*, 13355. Data for **11b**: mp 126–128 °C; ^{1}H NMR (60 MHz, $CDCl_3$) (Me_4Si) δ 2.9 (s, 1 H), 3.2 (d, 2 H), 3.8 (t, 1 H, buried), 3.8 (s, 1 H), 5.0 (s, 3 H), 7.3 (m, 4 H); MS *m/e* 230 (M^+), 215 (M^+ − 15), 204 (M^+ − 26), 171 (M^+ − 59), 144 (M − 86). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.80; H, 6.14; N, 12.16. Found: C, 67.65; H, 6.10; N, 12.13.

An Efficient and Stereoselective Synthesis of 2,3-Dihydroindoles via 1,5-Electrocyclization

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Received February 19, 1981

The indole moiety constitutes the central part of a large number of alkaloids. Novel methodology for the general synthesis of varied members of the indole alkaloid family therefore may concentrate on new strategies for the buildup of the indole nucleus.[1] In connection with the development of a general method for alkaloid synthesis on the basis of α-acyliminium intermediates,[2] it became necessary to contrive an efficient dihydroindole synthesis which was also required to possess a high degree of stereocontrol. The

(1) Representative references include the following: R. M. Coates and C. W. Hutchins, *J. Org. Chem.*, 44, 4742 (1979); R. B. Bard and J. F. Bunnett, *ibid.*, **45**, 1546 (1989); L. S. Hegedus, G. F. Allen, and E. L. Waterman, *J. Am. Chem. Soc.*, **98**, 2674 (1976); J. F. Wolfe, M. C. Sleevi, and R. R. Goehring, *ibid.*, **102**, 3646 (1980); Y. Ito, K. Kobayashi, and T. Saegusa, *ibid.*, **99**, 3532 (1977); H. Person, M. Del Aguila Pardo, and A. Foucaud, *Tetrahedron Lett.*, 281 (1980).

(2) W. N. Speckamp, *Int. Congr. Ser.—Excerpta Med.*, No. **457**, 50–61 (1979).

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Table I. Spirocyclization of Imine Arylsuccinimides 1

entry	imine	conditions[a]	yield, %[b]	product	mp, °C
1	1a	A	90	2a	158-160
2	1a	B	71	3a	217-219
3	1b	A	44	2b	219-222
4	1b	B (D[c]) (E[d])	81 (17) (38)	3b	179-181
5	1c	D[e] (E[f])	55 (59)	3c	170-173
6	1d	A (C)	21 (56)	2d	148.5-149
7	1d	B[g]	83	3d	125-126
8	1e	B	56	3e	173-174

[a] (A) EtOH-EtONa/room temperature. (B) *t*-BuOH-*t*-BuONa/room temperature. (C) Me_2SO-$NaOCH_3$/room temperature. (D) Benzene reflux, incomplete conversion. (E) Xylene reflux 18 h. [b] All values reported are isolated yields. [c] 21 days. [d] 18 h, incomplete. [e] 32 days. [f] 4 days. [g] Mixture of 5:1 THF-*t*-BuOH.

latter objective was reached through a new type of 1,5 electrocyclization[3] which amounts to the following process. Imines of type **1** undergo a spirocyclization reaction to *trans*-dihydroindoles[4] **2** or *cis*-dihydroindoles[4] **3** by merely stirring in a polar solvent at ambient temperature in the presence of a catalytic amount of base. *The stereochemistry of the latter cyclization is highly governed by the type of solvent used.*

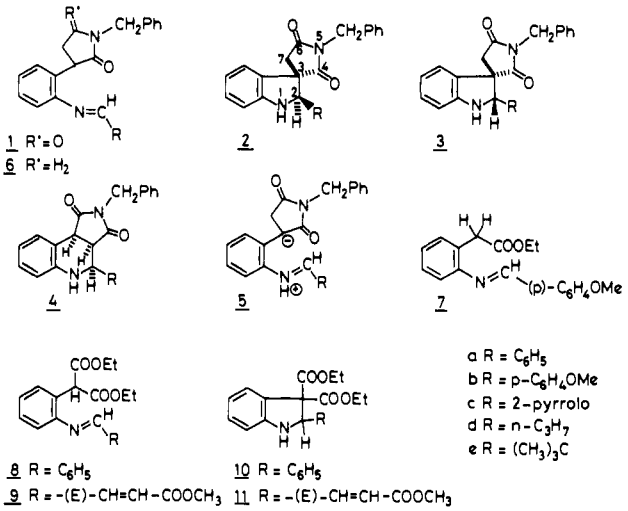
Addition of a toluene solution of **1a**[5] to a solution of EtOH/EtONa at room temperature and quenching with water after 4 min gave the *trans*-imide **2a** in 90% yield (Table I, entry 1). Most remarkably, when the reaction was carried out in *t*-BuOH/*t*-BuONa, the cis-product **3a** was obtained in 71% yield (entry 2, Table I) with no trace of **2a** being found.

For an evaluation of the scope of this novel ring closure, the cyclization of some representative aryl- and alkylimines **1** were studied. In every instance in *t*-BuOH/*t*-BuONa the isomers **3** were obtained (entries 4, 7, and 8, Table I) while in EtOH/EtONa (entries 3 and 6, Table I) or alternatively in Me_2SO/MeONa (entry 6, Table I) only the formation of the spirocyclic derivatives **2** could be proven. Stereoisomers **2** and **3** are not interconvertible by separate base treatment under the conditions of formation for each other. At 0 °C the spirocyclization of **1a** is complete within 4 min. At −20 °C in EtOH no reaction is observed, while in *t*-BuOH/THF the ring closure **1a** → **3a** still occurred. At higher temperatures, >30 °C, the selectivity of the reaction decreased and formation of byproducts, e.g., imide **4** started to interfere. The latter imide (**4**, R = n-C_3H_7) was also partly formed upon carrying out the reaction **1d** → **2d** in EtOH at room temperature. Its appearance can be understood in view of the small difference in kinetic acidity between CH and CH_2 groups of imide **1**.

Structure proof of imides **2** and **3** rests inter alia on ^{1}H NMR analysis. The chemical shifts of the characteristic AB patterns for the imide CH_2 protons is highly indicative of either trans- or cis-series **2** or **3**.[6] An X-ray analysis of **2a** unambiguously established the stereochemistry of series **2**.[7]

Of mechanistic significance is the observation that the spirocyclization of electron-rich arylimines also occurs in the absence of base by refluxing in an aromatic nonpolar solvent, albeit rather slowly (entries 4 and 5, Table I).

Chart I



Formally the spirocyclizations (**1** → **2**) and (**1** → **3**) can be viewed upon as 1,5-dipolar cyclizations.[8] Supposedly a facile proton transfer to the imine nitrogen results in the formation of the dipolar species **5** which may undergo a 1,5 electrocyclization. Obviously the latter process can also take place via the corresponding anion.[9] The consideration of the imine **1** as a phenyl homologue of a 1,3 dipole is supported by the recent observation of the 1,3-dipolar cycloadditions of structurally related imines of α-amino acid esters.[10] To account for the marked solvent-dependent stereochemistry, a relatively strong interaction between the alcohol and the reacting species has to be invoked. Although there are different polar sites at which complexation could occur, a likely possibility is the imine nitrogen–hydroxyl association. Earlier observations indicate a dramatic change of the preferred imine conformation in bulky alcoholic solvents.[11] A 1,5-dipolar cyclization of **5** starting from either *E*- or a *Z*-imine conformation could nicely explain the observed stereocontrol. Definite proof has to await further mechanistic studies.

A final comment on the necessary minimum acidity of the *o*-arylimine substituent is appropriate. While the imide **1** undergoes smooth ring closure, the corresponding amide imine **6** fails to cyclize. Somewhat surprising is the absence of any reaction of the ester imine **7** since its pK_a is of the same order of magnitude as the imide imine **1**. The diester imines **8** and **9**,[12] however, upon stirring in MeOH/MeONa at room temperature again afford the dihydroindole structures **10** and **11**,[13] a result which is of high prominence in connection with ongoing work in the total synthesis of mitomycins.[14] Further studies in this and related areas are actively pursued.

Acknowledgment. We thank P. Seignette and H. Schenk for the X-ray analysis of compound **2a**. The present investigation

(3) E. C. Taylor and I. J. Turchi, *Chem. Rev.*, **79**, 181 (1979); R. Huisgen, *Angew. Chem.*, **92**, 979 (1980); M. V. George, A. Mitra, and K. B. Sukumaran, *ibid.*, **92**, 1005 (1980).

(4) Prefixes cis and trans designate the stereochemical relationship between C-2 substituent and C-4 imide C=O group. A cis relation corresponds to the natural stereochemistry of dihydroindole alkaloids.

(5) Prepared by refluxing (*o*-aminophenyl)succinimide (1 mmol) [cf. J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 34, 2399 (1978)] with benzaldehyde (1.0–1.2 mmol) in 10 mL of toluene. For volatile aldehydes an excess (1.5–5 mmol) is used. The imine formation is effected by stirring in toluene over molecular sieves 4A at room temperature.

(6) Typical values for **2a**: C_7-CH_2(AB) δ 2.19, 2.38, 2.49, 2.67; **3a**: C_7-CH_2(AB) δ 2.92, 3.10, 3.24, 3.43; **2d**: C_7-CH_2(AB) δ 2.36, 2.54, 3.06, 3.25; **3d**: C_7-CH_2(AB) δ 2.58, 2.77, 3.08, 3.27.

(7) P. Seignette and H. Schenk, Laboratory for Crystallography, University of Amsterdam.

(8) For a related example: D. Lednicer and D. E. Emmert, *J. Heterocycl. Chem.*, **8**, 903 (1971).

(9) S. W. Staley in "Pericyclic Reactions", A. P. Marchand and R. E. Lehr, Eds., Academic Press, New York, 1977, pp 224–283.

(10) R. Grigg, J. Kemp, G. Sheldrick, and J. Trotter, *J. Chem. Soc., Chem. Commun.*, 109 (1978); R. Grigg, J. Kemp, J. Malone, and A. Tangthongkum, *ibid.*, 648 (1980).

(11) J. Bjorgo, D. R. Boyd, C. G. Watson, W. B. Jennings, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 2*, 1081 (1974).

(12) Prepared from diethyl (*o*-aminophenyl)malonate [cf. J. Bourdais and C. Germain, *Tetrahedron Lett.*, 195 (1970)] via NO_2 reduction (Pd-C/H_2) and coupling with the aldehyde.

(13) All compounds provided satisfactory spectral data and elemental analyses. Additional data for **10** and **11** are as follows. **10**: mp 70–72 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 and 1.29 (t, 6 H, CCH_3), 3.3–4.5 (m, 5 H, OCH_2, NH), 5.76 (s, 1 H, NCH), 6.6–7.5 (9 H). **11**: oil, ^{1}H NMR ($CDCl_3$) δ 1.21 and 1.31 (t, 6 H, CCH_3), 3.73 (s, OCH_3), 4.04–4.45 (5 H, OCH_2, NH), 5.18 (dd, 1 H, J = 1.0 and 7.0 Hz, NCH), 6.15 (dd, 1 H, J = 1.0 and 15.5 Hz, =CHCO), 6.6–7.5 (5 H).

(14) For a recent review, see K. Takahashi and T. Kametani, *Heterocycles*, 13, 411 (1979).

was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

A Stereoselective Synthesis of Indole Alkaloid Intermediates via *N*-Acyliminium Cyclizations

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Received February 19, 1981

N-Acyliminium ions have been recognized as valuable intermediates in heterocyclic synthesis.[1] Distinct advantages compared to the iminium counterpart include a favorable reactivity,[2] thus allowing carbon–carbon bond formation at ambient temperature and a highly improved stereocontrol[3] in the latter process.

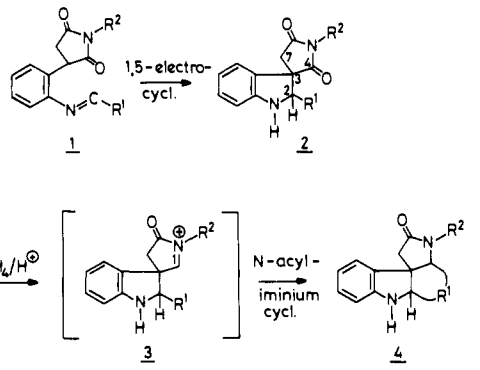
In the course of studies directed to a general and shortened synthesis of indole alkaloids of widely divergent nature, a novel and stereoselective 1,5-dipolar cyclization of imines **1** to dihydroindole 3,3-spiroimides **2**[4] was discovered. The imides **2** potentially serve as starting materials for the required carbinol lactams which in turn are the direct precursors[3] for the *N*-acyliminium ions **3**. The latter cationic centers are expected to initiate C–C bond formation with a variety of nucleophilic centers R′, thereby affording the annelated lactams **4** (Scheme I).

For an evaluation of the feasibility of utilizing a combined 1,5-electrocyclization (**1** → **2**) α-acyliminium ring closure (**3** → **4**) for the efficient construction of tetracyclic precursors of *Aspidosperma* alkaloids, the imine **1a** derived from phenylacetaldehyde and (*o*-aminophenyl)-*N*-benzylsuccinimide **5**[5] was spirocyclized to **2a**, mp 213.5–214.5 °C, upon treatment with a solution of *t*-BuONa/*t*-BuOH (yield 30%) (Scheme II).

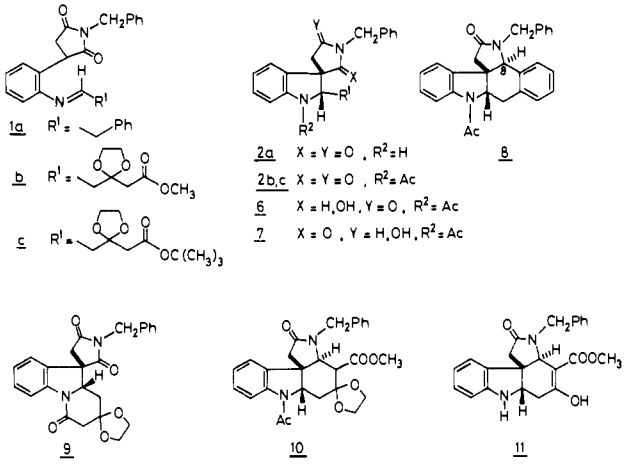
Experimental verification of the cis relationship between C-2 benzyl and C-4 imide carbonyl group in **2a** is derived in the following manner. After acylation (Ac_2O, room temperature) of **2a**, regioselective $NaBH_4/H^+$ reduction[6] afforded in 98% yield an epimeric mixture of hydroxy lactams **6a** and **7a** (3:1), easily distinguished on the basis of their ^1H NMR spectra. After fractional crystallization from EtOAc/hexane, **6a**, mp 142–147 °C, was cyclized (HCOOH/room temperature/18 h) to the novel pentacyclic structure **8**, mp 199–202 °C (EtOAc–hexane), in essentially quantitative yield as a single stereoisomer. The latter fact coupled with a prediction made on the basis of model studies of the least hindered cyclization pathway led to the proposed C-8 stereochemistry. Having confirmed the potential applicability of the combined approach, our attention was next focused on the synthesis of the alkaloid intermediate **11** for which the ketal esters **2b** and **2c** proved to be suitable starting materials. Upon spirocyclization of the imine **1b**[7] (*t*-BuONa/*t*-BuOH, room temperature) followed by N-acylation (Ac_2O, room temperature), the dihydroindole **2b**, mp 174–176 °C (EtOH), was obtained in 15% yield. Due to intramolecular N-acylation during the spirocyclization, the lactam **9**, mp 179–180 °C (EtOAc), was isolated as an unwanted byproduct in 45% yield. A solution for preventing the latter problem was found in the use of the *t*-Bu ester and a slight change in the type of base. Thus the imine **1c**[8] underwent cyclization [*t*-BuOLi in *t*-BuOH/THF (1:2)] and N-acylation (Ac_2O, room temperature) to **2c**, mp 150–152 °C (EtOH), in 84% yield.

After regioselective $NaBH_4/H^+$ reduction[6] of **2b**, a 2:1 mixture of hydroxy lactams **6b** and **7b** was formed which was separated by silica gel chromatography. The final ring closure of **6b**, mp 145–150 °C (EtOAc–hexane), to **10** was effected in 52% yield (*p*-TsOH–C_6H_6–glycol, reflux, 18 h), mp 204–206 °C (EtOAc–hexane). Alternatively **6b** could be converted quantitatively to **11**, mp 170–200 dec, by brief acid treatment (HCl–CH_3OH, reflux, 30 min). Similarly the hydroxy lactam **6c**, mp 214–219 °C, obtained by fractional crystallization (EtOAc) of the isomer mixture from the $NaBH_4/H^+$ reduction of **2c** afforded the enol ester **11** in 70% yield. Its structure was secured by conversion[10]

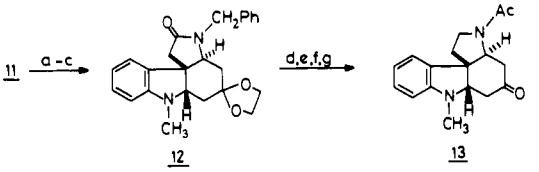
Scheme I



Scheme II



Scheme III[a]



[a] (a) aqueous HCl, (b) $H^+/HOCH_2CH_2OH$, (c) $CH_3I/NaHCO_3$, (d) LAH, (e) $H^+/H_2/Pd$–C, (f) Ac_2O, (g) H_3O^+.

(1) W. N. Speckamp, *Int. Congr. Ser.*—Excerpta *Med.*, No. 457, 50–61 (1979).
(2) (a) J. Dijkink and W. N. Speckamp, *Tetrahedron*, 34, 173 (1978); (b) H. E. Schoemaker, Tj. Boer-Terpstra, J. Dijkink, and W. N. Speckamp, *ibid.*, 36, 143 (1980).
(3) H. E. Schoemaker, J. Dijkink, and W. N. Speckamp, *Tetrahedron*, 34, 163 (1978).
(4) W. N. Speckamp, S. J. Veenstra, J. Dijkink, and H. P. Fortgens, *J. Am. Chem. Soc.*, preceding paper in this issue.
(5) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 34, 2399 (1978).
(6) J. B. P. A. Wijnberg, H. E. Schoemaker, and W. N. Speckamp, *Tetrahedron*, 34, 179 (1978).
(7) The aldehyde prepared by DIBAH reduction[9] of dimethyl acetonedicarboxylate ethylene ketal was coupled with **5** to afford **1b**.
(8) The aldehyde prepared by selective DIBAH reduction[9] of methyl *tert*-butyl acetonedicarboxylate ethylene ketal was coupled with **5** to afford **1c**.
(9) F. W. Brutcher, Jr. and H. Hinney, *Tetrahedron Lett.*, 697 (1979).

0002-7863/81/1503-4645$01.25/0