Chem. Pharm. Bull. **46**(5) 744—748 (1998) Vol. 46, No. 5

Synthesis of Octahydrobenzo[*b*]furans Using Tandem Conjugate Addition Reactions Initiated by Oxygen Nucleophile

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Received October 16, 1997; accepted November 26, 1997

When 1-nitrocyclohexene (1) was treated with methyl 4-hydroxy-2-butynoate (2) in the presence of potassium *tert*-butoxide in tetrahydrofuran–*tert*-butanol at 0 °C for 10 min, a tandem conjugate addition product, methyl *cis*-3a-nitrooctahydrobenzo[*b*]furan-$\Delta^{3,\alpha}$-acetate (3a), was obtained in quantitative yield as a 55 : 45 mixture of the (*Z*)- and (*E*)-isomers. The scope and limitations of this reaction were examined. Some transformation reactions of 3a are also described.

Key words tandem conjugate addition reaction; octahydrobenzo[*b*]furan; 1-nitrocyclohexene; methyl 4-hydroxy-2-butynoate; X-ray analysis

Tandem conjugate (Michael) addition reactions[1] are powerful tools for the construction of ring systems common to many natural products. In this sequence, a nucleophile adds to an activated alkene to produce a stabilized anion, which then adds to a second activated alkene (or alkyne) positioned so as to form a five- or six-membered ring. When the reaction is initiated by an oxygen nucleophile, it affords cyclic ethers, which have become of interest in recent years due to their widespread occurrence in nature and a wide range of biological activities.[2] However, such tandem reactions have received little attention.[3] In connection with our synthetic studies on avermectin antibiotics,[4] we have been interested in the synthesis of suitably functionalized octahydrobenzo[*b*]-furans. As a route to such compounds, we envisioned employing an oxygen nucleophile-initiated tandem conjugate addition reaction of cyclohexenes bearing an electron-withdrawing group at the 1-position with hydroxyalkynoates or hydroxyalkenoates. We selected 1-nitrocyclohexene (**1**) as an activated alkene, because nitroalkenes can function as good Michael acceptors and a variety of transformations are available for the nitro group incorporated into the product.[5] Herein we report a new synthesis of 3a-nitrooctahydrobenzo[*b*]furans **3** using the tandem conjugate addition reaction of **1** with methyl 4-hydroxy-2-butynoate and related compounds in the presence of a base. We also describe the transformation of compound **3a** thus obtained to the model compound **12** of the avermectins' southern portion.[6,7]

Results and Discussion

We began our investigations by examining the reaction of 1-nitrocyclohexene (**1**) with methyl 4-hydroxy-2-butynoate (**2a**)[8] in the presence of several bases. Since **2a** is unstable under the basic reaction conditions, two molar eq of **2a** was used. The yields of the products are based on **1**. When a solution of **1** and **2a** in dichloromethane (CH_2Cl_2) was treated with amine bases such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,1,3,3-tetramethylguanidine, poor yields (less than 27%) of 3a-nitrooctahydrobenzo[*b*]furan **3a**, or none, were obtained. Basic alumina also gave a low yield (8%) of **3a**. On the other hand, alkali metal bases such as sodium hydride (NaH) in CH_2Cl_2, butyllithium (BuLi) in tetrahydrofuran (THF), and potassium *tert*-butoxide (*tert*-BuOK) in THF–*tert*-BuOH were found to be effective. Among them, the best result was obtained when either a stoichiometric or catalytic amount of *tert*-BuOK was used in THF–*tert*-BuOH. The reaction was completed within 10 min at 0 °C to give **3a** in 97—100% yields as a mixture of the (*Z*)- and (*E*)-isomers in a ratio of 55 : 45. The isomers were separated by column chromatography on silica gel. The diastereoselectivity was slightly improved to 7 : 3 and 3 : 1 by using NaH/CH_2Cl_2 and BuLi/THF but the total yields decreased to 51 and 74%, respectively.

The structure and stereochemistry of (*Z*)- and (*E*)-**3a** were confirmed by X-ray analyses of both isomers (Fig. 1). The diagnostically useful features of the ^{1}H-NMR

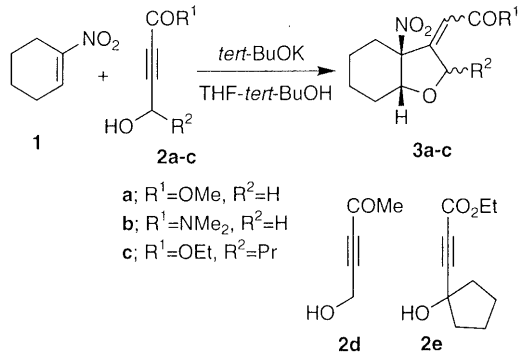

Chart 1

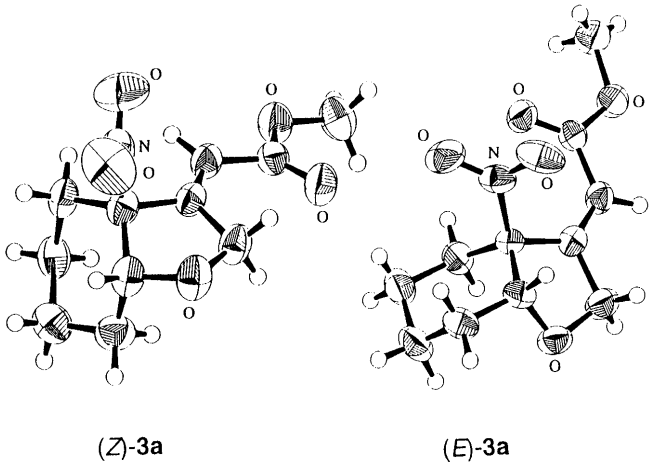

Fig. 1. ORTEP Drawings of (*Z*)- and (*E*)-**3a**

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Table 1. The ^{1}H-NMR Signals of the 2-H and Olefinic Protons of (*Z*)- and (*E*)-**3a**, **b**, and **c**

Compound	2-H	Olefinic H
(*Z*)-**3a**	4.84 (1H, dd, *J*=17.6, 2.9 Hz) 4.99 (1H, dd, *J*=17.6, 2.6 Hz)	6.05 (1H, t, *J*=2.7 Hz)
(*E*)-**3a**	4.70 (2H, d, *J*=2.2 Hz)	5.84 (1H, t, *J*=2.2 Hz)
(*Z*)-**3b**	4.86 (1H, dd, *J*=17.3, 2.9 Hz) 5.06 (1H, dd, *J*=17.3, 2.4 Hz)	6.39 (1H, t, *J*=2.7 Hz)
(*E*)-**3b**	4.65 (1H, dd, *J*=14.6, 2.0 Hz) 4.71 (1H, dd, *J*=14.6, 2.4 Hz)	6.19 (1H, t, *J*=2.1 Hz)
(*Z*)-**3c**	5.14 (1H, dt, *J*=9, 2 Hz)	6.02 (1H, d, *J*=2.4 Hz)
(*E*)-**3c**	4.65—4.72 (1H, m)	5.77 (1H, d, *J*=1.8 Hz)

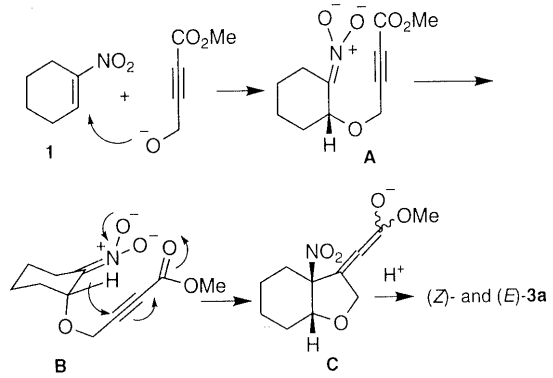

Chart 2

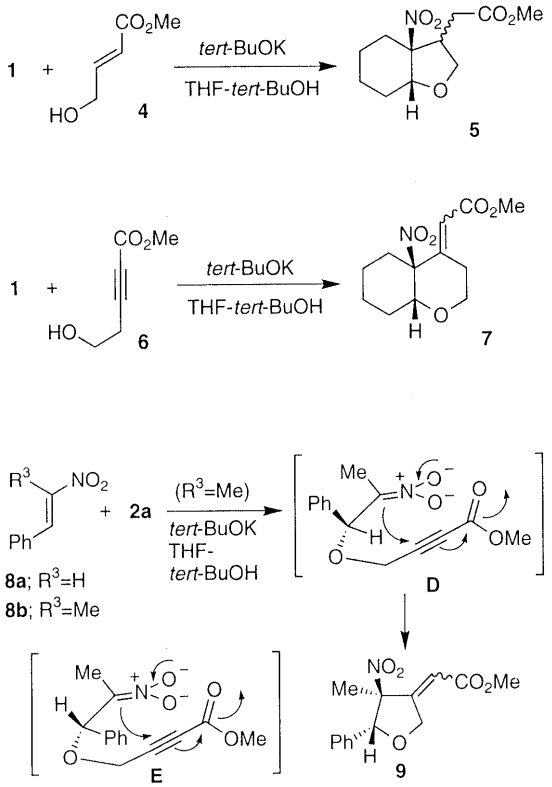

Chart 3

spectra of two geometrical isomers are the chemical shifts of the 2-H and olefinic proton signals. The 2-H protons in the (*Z*)-isomer appeared at lower field [δ 4.84 (1H) and 4.99 (1H)] than the same protons in the (*E*)-isomer [δ 4.70 (2H)] owing to the anisotropic effect of the ester carbonyl group. Similarly, the olefinic proton of the (*Z*)-isomer [δ 6.05 (1H)] occurred at lower field than that of the (*E*)-isomer [δ 5.84 (1H)] as a result of the influence of the nitro group (see Table 1).

The reaction of **1** with the amide **2b** also proceeded smoothly to give a mixture of (*Z*)- and (*E*)-**3b** in quantitative yield in a ratio of 55:45, and (*E*)-**3b** was obtained in a pure form by recrystallization. The stereochemistry of these isomers was assigned by a comparison of the chemical shifts of the 2-H and olefinic protons of the two isomers with those of (*Z*)- and (*E*)-**3a** (see Table 1). On the other hand, the reaction of **1** with the ketone **2d**[9] gave a complex mixture due to its lability to base.

The reaction of **1** with the secondary alcohol **2c** gave the octahydrobenzo[*b*]furan **3c** in 69% yield as an inseparable mixture of four possible isomers in a ratio of 50:28:13:9. The stereochemistry of the major two isomers was assigned as (*Z*)-ester for the first major isomer and (*E*)-ester for the second major isomer on the basis of the chemical shifts of the 2-H and olefinic protons of the two isomers (Table 1). The stereochemistry of the propyl group at the 2-position is unknown. The tertiary alcohol **2e**[10] failed to react with **1**, presumably because of crowding around the alkoxy anion.

These reactions may proceed by an initial addition[11] of the alkoxy anion to **1** to give the anion **A** which then undergoes second conjugate addition[12] through a transition state **B** leading to the anion **C** having the *cis* ring junction. Subsequent protonation affords (*Z*)- and (*E*)-**3a**. The transition state for formation of the *trans* ring junction would be highly strained.

1-Nitrocyclohexene (**1**) also reacted with a hydroxyalkenoate. Thus, treatment of **1** with methyl 4-hydroxy-2-butenoate (**4**)[13] under the same reaction conditions gave an inseparable mixture of two diastereoisomers of the octahydrobenzo[*b*]furans **5** in 81% yield and in a ratio of 4:1.

The tandem conjugate addition reaction of **1** was further extended to the synthesis of the six-membered ring. Thus, treatment of **1** with methyl 5-hydroxy-2-pentynoate (**6**)[14] gave the octahydrochromene **7** in 32% yield as a 2:1 mixture of the geometrical isomers. Although the exact stereochemistry of **5** and **7** is unknown, the mechanistic consideration described above suggests that all of these products have the *cis* ring junction.

We then examined the reaction of acyclic nitroalkenes **8a** and **8b**[15] with **2a**. When (*E*)-2-nitrostyrene (**8a**) was treated with **2a** in the presence of *tert*-BuOK in THF–*tert*-BuOH, only a complex mixture was obtained. On the other hand, (*E*)-2-methyl-2-nitrostyrene (**8b**), upon treatment with **2a** in the presence of *tert*-BuOH at 0 °C for 10 min, gave a mixture of (*Z*)- and (*E*)-3-methyl-3-nitro-2-phenyltetrahydrofurans [(*Z*)- and (*E*)-**9**] in 28 and 26% yields, respectively. The structure and stereochemistry of the oily (*Z*)-**9** were determined by differential nuclear Overhauser effect (NOE) experiments (Fig. 2), and those of crystalline (*E*)-**9** were confirmed by an X-ray analysis (Fig. 3). Interestingly, both isomers have the same stereochemistries at the 2- and 3-positions. This can be attributed to allylic 1,3-strain,[16] which makes conformer

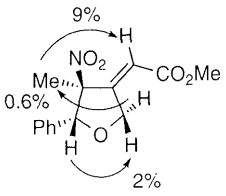

Fig. 2. The Result of NOE Experiments on (*Z*)-**9**

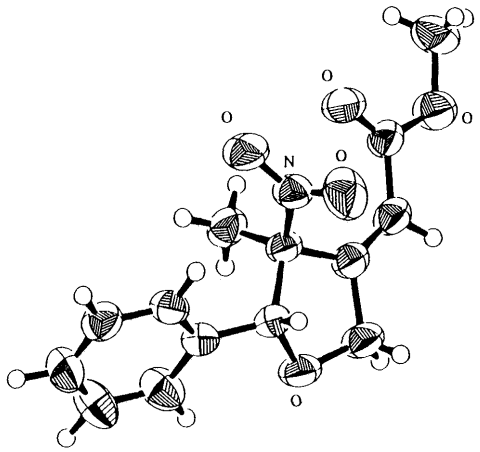

Fig. 3. ORTEP Drawing of (*E*)-**9**

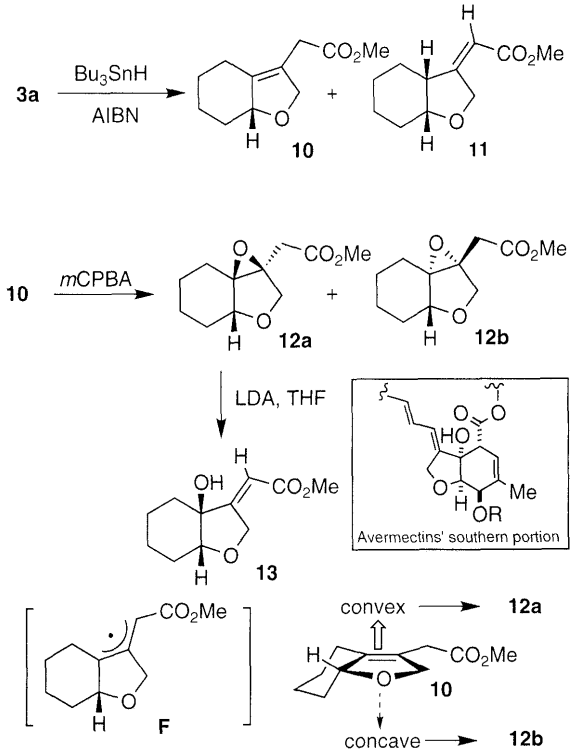

Chart 4

D the preferred transition state for the cyclization. An alternative conformer **E** is destabilized by a serious non-bonded repulsion between the oxygen atom of the nitro group and the phenyl group ($A^{1,3}$-strain) (Chart 3). A similar stereoselectivity has been observed in the reaction of acyclic nitroalkenes with 4-chlorobut-2-yn-1-ol.[7]

Finally, **3a** was converted into the model compound **12** of the avermectins' southern portion (Chart 4). Avermectins form a group of potent anthelmintic agents, and as such continue to attract much interest amongst synthetic chemists.[17] Thus, a mixture of **3a** was reduced with tributyltin hydride (Bu_3SnH) and azobis(isobutyronitrile) (AIBN) in boiling toluene[18] to give two isomeric olefins **10** and **11** in 57 and 29% yields, respectively. The structure of **10** was assigned on the basis of the absorption of the ester group at 1740 cm^{-1} in its IR spectrum and two AB quartets at δ 3.10 and 3.14 due to the methylene group adjacent to the ester group in its ^{1}H-NMR spectrum. The structure and stereochemistry of **11** were determined by NOE experiments: positive NOE effects were observed between the olefinic proton and 3a-H, and 3a-H and 7a-H. The observed selectivity of the formation of **10** and **11** can be rationalized in terms of the initially formed allylic radical intermediate F, which was reduced preferentially at the α-position to the ester group for electronic and steric reasons to give **10** as the major product.

Stereoselective epoxidation of **10** was accomplished with *m*-chloroperbenzoic acid (*m*CPBA) in toluene at $-23\,^\circ$C to give **12a** and **12b** in 57 and 22% yields, respectively. When the same reaction was carried out in CH_2Cl_2 at $-23\,^\circ$C, both the yield and selectivity slightly decreased to 70% and a 2:1 ratio. The stereochemical assignment of the major isomer **12a** was based on the assumption that the epoxidation would take place from the convex face of the double bond of **10**.[19] The oxirane ring opening of the major isomer **12a** with lithium diisopropylamide (LDA)[20] afforded **13** in 82% yield as a sole product. The stereochemistry of **13** was defined mainly by a comparison of the coupling pattern of the 2-H protons in the ^{1}H-NMR spectrum with those of **3a** and **11**.

In summary, this study revealed that a tandem conjugate addition reaction of 1-nitrocyclohexene with methyl 4-hydroxy-2-butynoate and related compounds provides a new route to 3a-nitrooctahydrobenzo[*b*]furans.

Experimental

All melting points are uncorrected. IR spectra were recorded using a JASCO IR-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. ^{13}C-NMR spectra were recorded on a Varian XL-300 (75 MHz) spectrometer using $CDCl_3$ as a solvent and are reported in ppm using solvent resonance as an internal standard (77.0 for $CDCl_3$). All ^{13}C-NMR spectra were determined with complete proton decoupling. High resolution mass spectra (exact MS and exact FAB-MS) were obtained with a JEOL JMS-SX 102A QQ instrument at 20 eV. Column chromatography was carried out on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure. Compounds **2a**,[8] **4**,[13] **6**,[14] and **8b**[15] were prepared according to the reported procedures.

Tandem Conjugate Addition Reaction of 1 with 2a General Procedure: A solution of *tert*-BuOK (45 mg, 0.4 mmol) in *tert*-BuOH (1 ml) was added to a solution of **1** (127 mg, 1 mmol) and **2a**[8] (228 mg, 2 mmol) in THF (2 ml) at 0 °C and the mixture was stirred for 10 min at the same temperature, then acidified with 10% HCl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1). The first fraction gave methyl *cis*-3a-nitrooctahydrobenzo[*b*]furan-(*Z*)-$\Delta^{3,\alpha}$-acetate [(*Z*)-**3a**] (129 mg, 53%) as colorless prisms, mp 63.0—63.5 °C (hexane–EtOAc). IR (KBr) cm^{-1}: 1720, 1670. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41—1.70 (4H, m), 1.75—1.87 (2H, m), 2.00—2.11 (1H, m), 2.44—2.56 (1H, m), 3.76 (3H, s, OCH_3), 4.66 (1H, t, J=5.2 Hz, 7a-H), 4.84 (1H, dd, J=17.6, 2.9 Hz, one of 2-H_2), 4.99 (1H, dd, J=17.6, 2.6 Hz, one of 2-H_2), 6.05 (1H, t, J=2.7 Hz, olefinic H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.1 (CH_2), 21.6 (CH_2), 25.7 (CH_2), 31.6 (CH_2), 51.8 (CH_3),

70.0 (2-CH_2), 78.7 (7a-CH), 94.0 (3a-C), 114.0 (=CHCO), 157.7 (3-C), 165.7 (ester CO). *Anal.* Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.77; H, 6.29; N, 5.70. The second fraction gave methyl *cis*-3a-nitrooctahydrobenzo[*b*]furan-(*E*)-$\Delta^{3,\alpha}$-acetate [(*E*)-**3a**] (105 mg, 44%) as colorless prisms, mp 114.0—114.5 °C (hexane–EtOAc). IR (KBr) cm^{-1}: 1720, 1670. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54—1.73 (5H, m), 1.90—2.17 (2H, m), 2.98 (1H, br d, J=15.6 Hz), 3.69 (3H, s, OCH_3), 4.27 (1H, br s, 7a-H), 4.70 (2H, d, J=2.2 Hz, 2-H_2), 5.84 (1H, t, J=2.2 Hz, olefinic H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 18.3 (CH_2), 21.0 (CH_2), 25.4 (CH_2), 28.3 (CH_2), 51.6 (CH_3), 72.0 (2-CH_2), 83.7 (7a-CH), 90.6 (3a-C), 112.5 (=CHCO), 158.9 (3-C), 164.6 (ester CO). *Anal.* Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.63; H, 6.24; N, 5.63.

Use of a Stoichiometric Amount of *tert*-BuOK as a Base: Compound **1** (127 mg, 1 mmol) was treated with **2a** (228 mg, 2 mmol) in the presence of *tert*-BuOK (224 mg, 2 mmol) in THF–*tert*-BuOH (2 : 1, 3 ml) at 0 °C for 30 min to give **3a** (241 mg, 100%, as a 55 : 45 mixture of the (*Z*)-and (*E*)-isomers).

Use of NaH as a Base: Compound **1** (127 mg, 1 mmol) was treated with **2a** (228 mg, 2 mmol) in the presence of NaH (60% in mineral oil, 80 mg, 2 mmol) in CH_2Cl_2 (3 ml) at 0 °C for 30 min to give **3a** (122 mg, 51%, as a 7 : 3 mixture of the (*Z*)-and (*E*)-isomers).

Use of BuLi as a Base: Compound **1** (56 mg, 0.44 mmol) was treated with **2a** (100 mg, 0.88 mmol) in the presence of BuLi (1.6 M in hexane, 0.55 ml, 0.88 mmol) in THF (3 ml) at 0 °C for 30 min to give **3a** (78 mg, 74%, as a 3 : 1 mixture of the (*Z*)-and (*E*)-isomers).

4-Hydroxy-*N*,*N*-dimethyl-2-butynamide (2b) A solution of BuLi (1.6 M in hexane, 5 ml, 8 mmol) was added to a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (700 mg, 5 mmol) in THF (15 ml) at −78 °C and the mixture was stirred for 30 min. Then a solution of *N*,*N*-dimethylcarbamyl chloride (1.08 g, 10 mmol) in THF (1 ml) was added at the same temperature and the whole was stirred for an additional 30 min and at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with Et_2O (3 × 20 ml). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–EtOAc, 1 : 1) to give the corresponding amide (845 mg, 80%), which was treated with pyridinium *p*-toluenesulfonate (101 mg, 0.4 mmol) in methanol (10 ml) at room temperature. After usual work-up, the crude compound was chromatographed on silica gel (hexane–EtOAc, 1 : 2) to give **2b** (278 mg, 55%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3300—3600, 2240, 1620. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.97 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.4—3.9 (1H, br, OH), 4.43 (2H, s, CH_2). Exact MS *m*/*z*: 127.0639 (Calcd for $C_6H_9NO_2$: 127.0633).

Tandem Conjugate Addition Reaction of 1 with 2b Following the general procedure, **1** (127 mg, 1 mmol) was treated with **2b** (191 mg, 1.5 mmol) in the presence of *tert*-BuOK (45 mg, 0.4 mmol) and the crude material was chromatographed on silica gel (hexane–EtOAc, 1 : 2) to give a 55 : 45 mixture of (*Z*)- and (*E*)-isomers of *N*,*N*-dimethyl-*cis*-3a-nitrooctahydrobenzo[*b*]furan-$\Delta^{3,\alpha}$-acetamide (**3b**) (254 mg, 100%) as a white solid. Recrystallization of the mixture from hexane–EtOAc gave pure (*E*)-isomer as colorless prisms, mp 144.5—146.0 °C. IR (CCl_4) cm^{-1}: 1620. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.50—2.08 (8H, m), 2.93 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 4.30 (1H, t, J=3.1 Hz, 7a-H), 4.65 (1H, dd, J=14.6, 2.0 Hz, one of 2-H_2), 4.71 (1H, dd, J=14.6, 2.4 Hz, one of 2-H_2), 6.19 (1H, t, J=2.1 Hz, olefinic H). *Anal.* Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 57.05; H, 7.25; N, 11.08. The ^{1}H-NMR spectrum of the mixture of (*Z*)- and (*E*)-**3b** exhibited the following signals of the (*Z*)-isomer, δ: 2.99 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 4.64 (1H, t, J=4.7 Hz, 7a-H), 4.86 (1H, dd, J=17.3, 2.9 Hz, one of 2-H_2), 5.06 (1H, dd, J=17.3, 2.4 Hz, one of 2-H_2), 6.39 (1H, t, J=2.7 Hz, olefinic H).

Ethyl 4-Hydroxy-2-heptynoate (2c) According to the procedure of Midland *et al.*,[10] a solution of BuLi (1.6 M in hexane, 3.4 ml, 5.5 mmol) was added to a solution of ethyl propiolate (490 mg, 5 mmol) in THF–Et_2O–pentane (4 : 1 : 1, 10 ml) at −100 °C and the mixture was stirred for 20 min. Then a solution of butyraldehyde (397 mg, 5.5 mmol) in THF–Et_2O–pentane (4 : 1 : 1, 2 ml) was added at the same temperature and the whole was stirred for an additional 20 min. The mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with Et_2O (3 × 20 ml). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–EtOAc, 10 : 1) to give **2c** (315 mg, 37%) as a colorless oil. IR (CCl_4) cm^{-1}: 3600—3300, 2240, 1710. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=6 Hz, CH_3), 1.29 (3H, t, J=7 Hz, OCH_2CH_3), 1.3—1.8 (4H, m), 2.4—2.7 (1H, m, OH), 4.20 (2H, q, J=7 Hz, OCH_2CH_3), 4.2—4.5 (1H, m, 4-H). Exact FAB-MS *m*/*z*: 171.1024 (Calcd for $C_9H_{15}O_3+H^+$: 171.1021).

Tandem Conjugate Addition Reaction of 1 with 2c Following the general procedure, **1** (92 mg, 0.72 mmol) was treated with **2c** (245 mg, 1.44 mmol) in the presence of *tert*-BuOK (32 mg, 0.29 mmol) and the crude material was chromatographed on silica gel (hexane–EtOAc, 20 : 1) to give a 50 : 28 : 13 : 9 mixture of ethyl *cis*-3a-nitro-2-propyloctahydrobenzo[*b*]furan-$\Delta^{3,\alpha}$-acetate (**3c**) (148 mg, 69%) as a colorless oil. IR (CCl_4) cm^{-1}: 1715, 1665. ^{1}H-NMR (300 MHz, $CDCl_3$) for the first major isomer δ: 0.95 (3H, t, J=7.2 Hz, CH_3), 1.32 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.37—1.73 (8H, m), 1.73—2.20 (3H, m), 2.30—2.42 (1H, m), 4.22 (2H, q, J=7.2 Hz, OCH_2CH_3), 4.83 (1H, t, J=5.9 Hz, 7a-H), 5.14 (1H, dt, J=9, 2 Hz, 2-H), 6.02 (1H, d, J=2.4 Hz, olefinic H). Selected signals for the second major isomer δ: 0.99 (3H, t, J=7.2 Hz, CH_3), 1.25 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.14 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.38 (1H, br s, 7a-H), 4.65—4.72 (1H, m, 2-H), 5.77 (1H, d, J=1.8 Hz, olefinic H). Selected signals for the third major isomer δ: 0.97 (3H, t, J=7.0 Hz, CH_3), 1.28 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.17 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.61 (1H, br s, 7a-H), 5.04—5.11 (1H, m, 2-H), 5.82 (1H, d, J=2.8 Hz, olefinic H). Selected signal for the minor isomer δ: 5.75 (1H, d, J=2.4 Hz, olefinic H). *Anal.* Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 61.07; H, 7.88; N, 4.53. The ratio of stereoisomers of **3c** was estimated from the integrated intensity of the peak heights of the signals due to the olefinic protons at δ 6.02 (d), 5.77 (d), 5.82 (d), and 5.75 (d), respectively.

Tandem Conjugate Addition Reaction of 1 with 4 Following the general procedure, **1** (64 mg, 0.5 mmol) was treated with **4**[13] (87 mg, 0.75 mmol) in the presence of *tert*-BuOK (56 mg, 0.5 mmol) and the crude material was chromatographed on silica gel (hexane–EtOAc, 10 : 1) to give a 4 : 1 mixture of methyl *cis*-3a-nitrooctahydrobenzo[*b*]furan-3-acetate (**5**) (99 mg, 81%) as a colorless oil. IR (CCl_4) cm^{-1}: 1740. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.20—2.07 (7H, m), 2.31—2.56 (3H, m), 2.75—2.89 (1H, m), 3.56—3.71 (1H, m, one of 2-H_2), 3.67 (1/5 × 3H, s, OCH_3 of the minor isomer), 3.68 (4/5 × 3H, s, OCH_3 of the major isomer), 4.30—4.42 (1H, m, one of 2-H_2), 4.43—4.47 (4/5 × 1H, m, 7a-H of the major isomer), 4.47—4.52 (1/5 × 1H, m, 7a-H of the minor isomer). *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.60; H, 7.18; N, 5.77.

Tandem Conjugate Addition Reaction of 1 with 6 Following the general procedure, **1** (127 mg, 1 mmol) was treated with **6**[14] (144 mg, 1.5 mmol) in the presence of *tert*-BuOK (112 mg, 1 mmol) and the crude material was chromatographed on silica gel (hexane–EtOAc, 10 : 1) to give a 2 : 1 mixture of methyl *cis*-4a-nitrooctahydro-4*H*-chromene-$\Delta^{4,\alpha}$-acetate (**7**) (82 mg, 32%) as a colorless oil. IR (CCl_4) cm^{-1}: 1720, 1640. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.20—2.80 (10H, m), 3.61 (2/3 × 1H, td, J=11.4, 3.2 Hz, one of 2-H_2 of the major isomer), 3.66 (1/3 × 3H, s, OCH_3 of the minor isomer), 3.70 (2/3 × 3H, s, OCH_3 of the major isomer), 3.74 (1/3 × 1H, ddd, J=12.0, 11.2, 3.1 Hz, one of 2-H_2 of the minor isomer), 3.94—3.99 (1/3 × 1H, m, 8a-H of the minor isomer), 4.12 (1/3 × 1H, ddd, J=11.2, 6.3, 2.0 Hz, one of 2-H_2 of the minor isomer), 4.13 (2/3 × 1H, ddd, J=11.4, 6.3, 2.4 Hz, one of 2-H_2 of the major isomer), 4.36 (2/3 × 1H, t, J=3.2 Hz, 8a-H of the major isomer), 5.55 (2/3 × 1H, d, J=1.5 Hz, olefinic H of the major isomer), 5.84 (1/3 × 1H, dd, J=2.2, 1.0 Hz, olefinic H of the minor isomer). *Anal.* Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.66; H, 6.88; N, 5.47.

Tandem Conjugate Addition Reaction of 8b with 2a Following the general procedure, **8b**[15] (114 mg, 1 mmol) was treated with **2a** (326 mg, 2 mmol) in the presence of *tert*-BuOK (45 mg, 0.4 mmol) and the crude material was chromatographed on silica gel (hexane–EtOAc, 10 : 1). The first fraction gave methyl (2*R**,3*S**)-3-methyl-3-nitro-2-phenyltetrahydrofuran-(*Z*)-$\Delta^{4,\alpha}$-acetate [(*Z*)-**9**] (63 mg, 28%) as a colorless oil. IR (CCl_4) cm^{-1}: 1720, 1660. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 5.00 (1H, dd, J=17.3, 2.9 Hz, one of 5-H_2), 5.33 (1H, dd, J=17.3, 2.4 Hz, one of 5-H_2), 5.68 (1H, s, 2-H), 5.98 (1H, t, J=2.2 Hz, olefinic H), 7.22—7.30 (2H, m, Ar-H), 7.33—7.41 (3H, m, Ar-H). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.29; H, 5.51; N, 4.96. The second fraction gave methyl (2*R**,3*S**)-3-methyl-3-nitro-2-phenyltetrahydrofuran-(*E*)-$\Delta^{4,\alpha}$-acetate [(*E*)-**9**] (60 mg, 26%) as colorless prisms, 93.0—94.0 °C (hexane–EtOAc). IR (CCl_4) cm^{-1}: 1735, 1680. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.86 (1H, dd, J=15.5, 2.0 Hz, one of 5-H_2), 4.89 (1H, dd, J=15.5, 2.5 Hz, one of 5-H_2), 5.22 (1H, s, 2-H), 6.00 (1H, t,

$J=2.2$ Hz, olefinic H), 7.18—7.26 (2H, m, Ar-H), 7.34—7.42 (3H, m, Ar-H). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.45; H, 5.40; N, 4.95.

Crystal Structure Determination[21] Single crystals of (*Z*)- and (*E*)-**3a**, and (*E*)-**9** were obtained by recrystallization from hexane–EtOAc. Crystal data of (*Z*)-**3a**: $C_{11}H_{15}NO_5$, M.W.=241.24, colorless needles, monoclinic, space group $P2_1/c$, $a=6.4085$ (7) Å, $b=26.654$ (5) Å, $c=7.5127(8)$ Å, $V=1163.8(3)$ Å^3, $Z=4$, $D_{calc}=1.377$ g cm^{-3}, $\mu(CuK\alpha)=9.28$ cm^{-1}. The R (R_w) value of (*Z*)-**3a** was 0.039 (0.062). Crystal data of (*E*)-**3a**: $C_{11}H_{15}NO_5$, M.W.=241.24, colorless prisms, monoclinic, space group $P2_1/c$, $a=9.784(1)$ Å, $b=10.271(1)$ Å, $c=11.557(1)$ Å, $V=1157.4(2)$ Å^3, $Z=4$, $D_{calc}=1.384$ g cm^{-3}, $\mu(CuK\alpha)=9.33$ cm^{-1}. The R (R_w) value of (*E*)-**3a** was 0.035 (0.055). Crystal data of (*E*)-**9**: $C_{14}H_{15}NO_5$, M.W.=277.28, colorless prisms, triclinic, space group $P\bar{1}$, $a=12.0949(9)$ Å, $b=16.619(2)$ Å, $c=7.4647(6)$ Å, $V=1407.3(2)$ Å^3, $Z=4$, $D_{calc}=1.309$ g cm^{-3}, $\mu(CuK\alpha)=8.44$ cm^{-1}. The R (R_w) value of (*E*)-**9** was 0.059 (0.109). The data were collected on a Rigaku AFC7R diffractometer at 23 ± 1 °C using graphite-monochromated Cu$K\alpha$ ($\lambda=1.54178$ Å) radiation. The structure was solved by direct methods (program SIR92[22] for (*Z*)-**3a**, SAPI91[23] for (*E*)-**3a**, and MITHRIL90[24] for (*E*)-**9**) and expanded using Fourier techniques (program DIRDIF94[25]). The non-hydrogen atoms were refined anisotropically, including hydrogen atoms. Hydrogen atoms were refined isotropically for (*E*)-**3a** but not refined for (*Z*)-**3a** and (*E*)-**9**. Neutral atom scattering factors were taken from Cromer and Waber.[26] All calculations were performed using the teXsan[27] crystallographic software package of Molecular Structure Corporation.

Methyl 2,4,5,6,7,7a-Hexahydrobenzo[*b*]furan-3-acetate (10) and Methyl *cis*-Octahydrobenzo[*b*]furan-(*Z*)-$\Delta^{3,\alpha}$-acetate (11) A solution of **3a** (800 mg, 3.3 mmol), Bu_3SnH (1.44 g, 4.95 mmol), and AIBN (7 mg, 0.165 mmol) in toluene (15 ml) was refluxed for 2 h. After concentration, the residue was chromatographed on silica gel (hexane–EtOAc, 10 : 1). The first fraction gave **11** (186 mg, 29%) as a colorless oil. IR (CCl_4) cm^{-1}: 1720, 1680. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21—1.89 (8H, m), 2.61—2.71 (1H, m, 3a-H), 3.71 (3H, s, OCH_3), 3.95—4.01 (1H, m, 7a-H), 4.68 (1H, dd, $J=17.8$, 2.6 Hz, one of 2-H_2), 4.94 (1H, dt, $J=17.8$, 1.9 Hz, one of 2-H_2), 5.75 (1H, td, $J=2.6$, 1.5 Hz, olefinic H). Exact MS *m/z*: 196.1081 (Calcd for $C_{11}H_{16}O_3$: 196.1100). The second fraction gave **10** (368 mg, 57%). IR (CCl_4) cm^{-1}: 1740. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53—1.95 (6H, m), 2.10—2.19 (1H, m), 2.49—2.58 (1H, m), 3.10, 3.14 (1H each, ABq, $J=15.8$ Hz, CH_2CO), 3.69 (3H, s, OCH_3), 4.50—4.71 (3H, m, 2-H_2, 7a-H). Exact MS *m/z*: 196.1105.

Methyl (1a*S,3a*R**,7a*R**)- and (1a*R**,3a*R**,7a*S**)-Hexahydro-5*H*-oxireno[*c*]benzofuran-1a-acetates (12a and 12b)** A solution of **10** (50 mg, 0.25 mmol) in toluene (1 ml) was added to a suspension of *m*CPBA (88 mg, 0.51 mmol) in toluene (2 ml) at −78 °C. The mixture was stirred for 22 h at −23 °C and diluted with EtOAc (10 ml). The mixture was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane–EtOAc, 3 : 1). The first fraction gave **12b** (12 mg, 22%). IR (CCl_4) cm^{-1}: 1740. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21—1.47 (2H, m), 1.58—1.90 (4H, m), 1.94—2.19 (2H, m), 2.71 and 2.86 (1H each, ABq, $J=16.6$ Hz, CH_2CO), 3.74 (3H, s, OCH_3), 3.88—3.97 (1H, m, 3a-H), 3.90 and 4.04 (1H each, ABq, $J=10.3$ Hz, 2-H_2). Exact FAB-MS *m/z*: 213.1136 (Calcd for $C_{11}H_{16}O_4+H^+$: 213.1126). The second fraction gave **12a** (30 mg, 57%). IR (CCl_4) cm^{-1}: 1740. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23—1.92 (7H, m), 2.01—2.11 (1H, m), 2.78 and 2.83 (1H each, ABq, $J=16.5$ Hz, CH_2CO), 3.53 (1H, dd, $J=11.4$, 4.8 Hz, 3a-H), 3.73 (3H, s, OCH_3), 3.65 and 4.05 (1H each, ABq, $J=10.2$ Hz, 2-H_2). Exact FAB-MS *m/z*: 213.1151.

Methyl *cis*-3a-Hydroxyoctahydrobenzo[*b*]furan-(*E*)-$\Delta^{3,\alpha}$-acetate 13 A solution of LDA (1.5 M in hexane, 0.17 ml, 0.25 mmol) was added to a solution of **12a** (45 mg, 0.21 mmol) in THF (4.5 ml) at −78 °C and the mixture was stirred at the same temperature for 10 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (3×10 ml). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–EtOAc, 3 : 1) to give **13** (37 mg, 82%) as colorless crystals, mp 115.5—116.0 °C (hexane–EtOAc). IR (KBr) cm^{-1}: 3600—3300, 1720, 1680. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17—2.18 (9H, m, $4\times CH_2$, OH), 3.19 (1H, dd, $J=11.7$, 4.1 Hz, 7a-H), 3.74 (3H, s, OCH_3), 4.65 (1H, dd, $J=17.6$, 2.6 Hz, C_2-H), 4.94 (1H, ddd, $J=17.6$, 2.6, 0.8 Hz, 2-H), 5.85 (1H, t, $J=2.6$ Hz, olefinic H). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.42; H, 7.67.

Acknowledgments The authors are grateful to Dr. M. Yamashita, Kyoto Pharmaceutical University, for the X-ray analyses.

References and Notes

1) Tietze L. F., Beifuss U., *Angew. Chem. Int. Ed. Engl.*, **32**, 131—163 (1993); Ihara M., Fukumoto K., *ibid.*, **32**, 1010—1022 (1993); Bunce R. A., *Tetrahedron*, **51**, 13103—13159 (1995).
2) Boivin T. L. B., *Tetrahedron*, **43**, 3309—3362 (1987); Harmange J.-C., Figadère B., *Tetrahedron: Asymmetry*, **4**, 1711—1754 (1993).
3) Very recently, palladium-mediated tandem conjugate addition reactions of benzylidenemalonates with allyl and propargyl alcohols to form tetrahydrofurans have been reported: Cavicchioli M., Sixdenier E., Derrey A., Bouyssi D., Balme G., *Tetrahedron Lett.*, **38**, 1763—1766 (1997); Marat X., Monteiro N., Balme G., *Synlett*, **1997**, 845—847.
4) Yakura T., Yoshida D., Ueki A., Nakao K., Ikeda M., *Chem. Pharm. Bull.*, **45**, 651—658 (1997).
5) Yoshikoshi A., Miyashita M., *Acc. Chem. Res.*, **18**, 284—290 (1985); Barrett A. G. M., Graboski G. G., *Chem. Rev.*, **86**, 751—762 (1986).
6) A part of this work has appeared as a preliminary communication: Yakura T., Tsuda T., Matsumura Y., Yamada S., Ikeda M., *Synlett*, **1996**, 985—986.
7) Very recently, the synthesis of 3-vinylidenetetrahydrofurans using a similar tandem Michael addition-S_N2' substitution of nitroalkenes with 4-chlorobut-2-yn-1-ol has been reported: Dulcère J.-P., Dumez E., *Chem. Commun.*, **1997**, 971—972; also see, Dumez E., Rodriguez J., Dulcère J.-P., *ibid.*, **1997**, 1831—1832.
8) Earl R. A., Townsend L. B., *Can. J. Chem.*, **58**, 2550—2561 (1980).
9) Larock R. C., Liu C.-L., *J. Org. Chem.*, **48**, 2151—2158 (1983).
10) Midland M. M., Tramontano A., Cable J. R., *J. Org. Chem.*, **45**, 28—29 (1980).
11) Kamimura A., Ono N., *Tetrahedron Lett.*, **30**, 731—734 (1989); Duffy J. L., Kurth J. A., Kurth M. J., *ibid.*, **34**, 1259—1260 (1993).
12) Ono N., Miyake H., Kamimura A., Tsukui N., Kaji A., *Tetrahedron Lett.*, **23**, 2957—2960 (1982); Ono N., Kamimura A., Kaji A., *Synthesis*, **1984**, 226—227.
13) Tufariello J. J., Tette J. P., *J. Org. Chem.*, **40**, 3866—3869 (1975).
14) Piers E., Chong J. M., Morton H. E., *Tetrahedron*, **45**, 363—380 (1989).
15) Ono N., Miyake H., Kamimura A., Hamamoto I., Tamura R., Kaji A., *Tetrahedron*, **41**, 4013—4023 (1985).
16) Hoffmann R. W., *Chem. Rev.*, **89**, 1841—1860 (1989).
17) Davies H. G., Green R. H., *Chem. Soc. Rev.*, **20**, 211—269, 271—339 (1991); Peak S. A., Smith A. B., III, "Studies in Natural Products Chemistry," Vol. 12, ed. by Atta-ur-Rahman, Elsevier, Amsterdam, 1993, pp. 3—33; A recent report on the synthesis of avermectin–milbemycin antibiotics: Steel P. G., Mills O. S., Parmee E. R., Thomas E. J., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 391—400, and references cited therein.
18) Ono N., Miyake H., Tamura R., Kaji A., *Tetrahedron Lett.*, **22**, 1705—1708 (1981).
19) Stereoselective oxidation of the related silyl enol ether was reported, see: Fujiwara S., Smith A. B., III, *Tetrahedron Lett.*, **33**, 1185—1188 (1992).
20) Crandall J. K., Lin L.-H. C., *J. Org. Chem.*, **33**, 2375—2378 (1968).
21) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
22) Altomare A., Cascarano G., Giacovazzo C., Guagliardi A., Burla M. C., Polidori G., Camalli M., *J. Appl. Cryst.*, **7**, 435 (1994).
23) SAPI91: Fan H.-F. (1991). Structure Analysis Programs with Intelligent Control, Rigaku Corporation, Tokyo, Japan.
24) MITHRIL90: Gilmore C. J. (1990). An integrated direct methods computer program. Univ. of Glasgow, Scotland.
25) DIRDIF94: Beurskens P. T., Admiraal G., Beurskens G., Bosman W. P., de Gelder R., Israel R., Smits J. M. M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.
26) Cromer D. T., Waber J. T., "International Tables for X-ray Crystallography," Vol. 4, The Kynoch Press, Birmingham, 1974, Table 2.2 A.
27) teXan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992).