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An efficient synthesis of open chain nitroalcohols by regioselective ring opening of cyclic *tert*-β-nitroalcohols by sodium borohydride: Short synthesis of (±)-tridecan-12-olide and (±)-9-tetradecanolide

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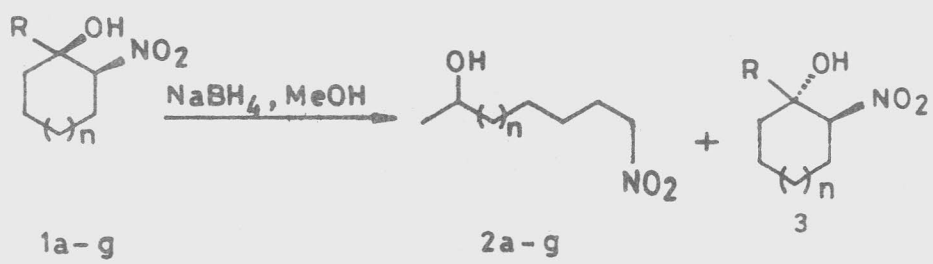
It has been demonstrated that a wide variety of cyclic *tert*-β-nitroalcohols can be efficiently cleaved regioselectively using stoichiometric amount of $NaBH_4$ in organic solvents like dry MeOH, Et_2O, CH_3CN etc. giving open chain secondary nitroalcohols such as $RCH(OH)(CH_2)_nCH_2NO_2$ where R is alkyl, aryl etc. and n=4,5, etc. The utility of this reaction has been demonstrated by achieving short syntheses of naturally occurring (±)-tridecan-12-olide and (±)-9-tetradecanolide.

In recent years aliphatic nitro compounds have emerged as versatile reaction intermediates and building blocks in organic synthesis[1]. In particular α-nitro ketones have been found to have remarkable synthetic potential because these compounds undergo a variety of reactions viz. a) transposition of ketone carbonyl[2], b) ring cleavage of C(1)- C(2) bond by external electrophiles[3], c) 'zip' reaction[4] to effect cyclic rearrangements and d) their unusual reactivity towards Grignard reagents giving exclusively the *trans-tert*-β-nitroalcohols[5]. In continuation of our interest on the chemistry of cyclic α-nitro ketones and their derivatives[6,7], we have recently demonstrated that a wide variety of *tert*-β-nitroalcohols can be cleaved very efficiently by refluxing with anhyd. copper sulfate adsorbed on silica gel in dry benzene giving the open chain ω-keto nitro aliphatics exclusively. We have recently observed that when *tert*-β-nitroalcohols **1a-g** are treated with stoichiometric amount of $NaBH_4$ in organic solvents like MeOH, Et_2O, CH_3CN etc., the bond between the carbon bearing the tertiary hydroxy group and the carbon bearing the nitro group cleaves giving acyclic nitroalcohols **2a-g** in high yields (Scheme I).

Ballini *et al* have reported[8] the ring cleavage of cyclic α-nitro ketones on treatment with large excess (5 equiv.) of $NaBH_4$ in acetonitrile water system which presumably proceeds via intermediate cyclic α-nitroalcohols. Both Ballini *et al.*[9] and Dampawan *et al.*[10] have also reported synthesis of cyclic vinyl nitro compounds from cyclic α-nitroketones via a two steps sequence where they actually isolated the intermediate α-nitroalcohols showing that secondary nitroalcohols are not effected on treatment with $NaBH_4$.

We observed that this cleavage reaction is highly solvent dependant. Although the yield of **2a** was found to be high in dry MeOH, or dry Et_2O, no trace of **2a** was detected when the reaction was carried out in the presence of MeOH-water mixture; in which case 50% conversion of **1a** to its isomeric

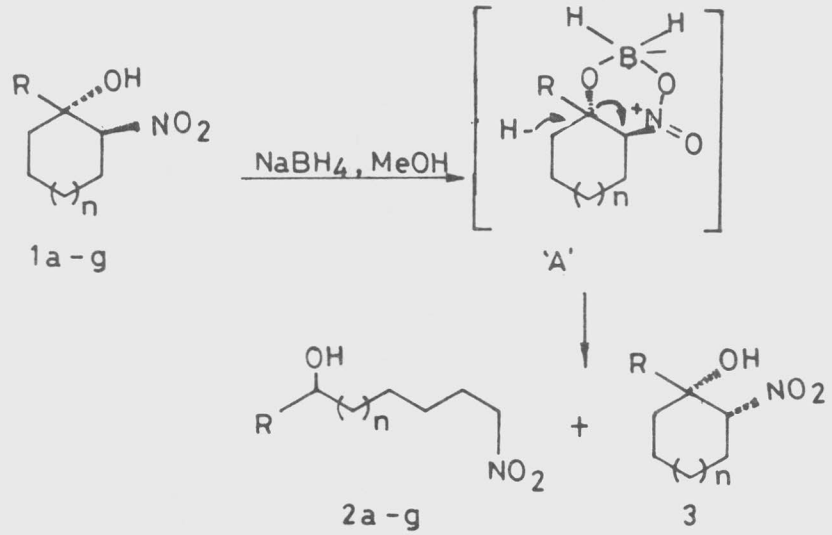


product **3a** was observed. On the other hand when the reaction was carried out in CH_3CN/H_2O mixture, exclusive formation of **2a** was only observed. When the reaction was carried out in anhyd. methanol using only half the stoichiometric amount of $NaBH_4$, the major product was **2a** along with **3a** and a trace amount of 7-nitroheptan-2-one.

We have proposed a plausible mechanism by which the chemoselectivity of the cleavage and hydride delivery system displayed by $NaBH_4$ can be explained. The reaction involves an initially formed boron complex `A' intermediate in which the boron atom can almost exclusively coordinate to the proximate nitro group which is crucial for chemoselectivity. Intramolecular hydride transfer to electron deficient carbon bearing the tertiary hydroxyl group takes place initially which facilitates the labile C(1)-C(2) bond to break. Finally intermolecular quench of the nitronate anion by proton transfer from the solvent yields the desired secondary nitro alcohols (Scheme I).

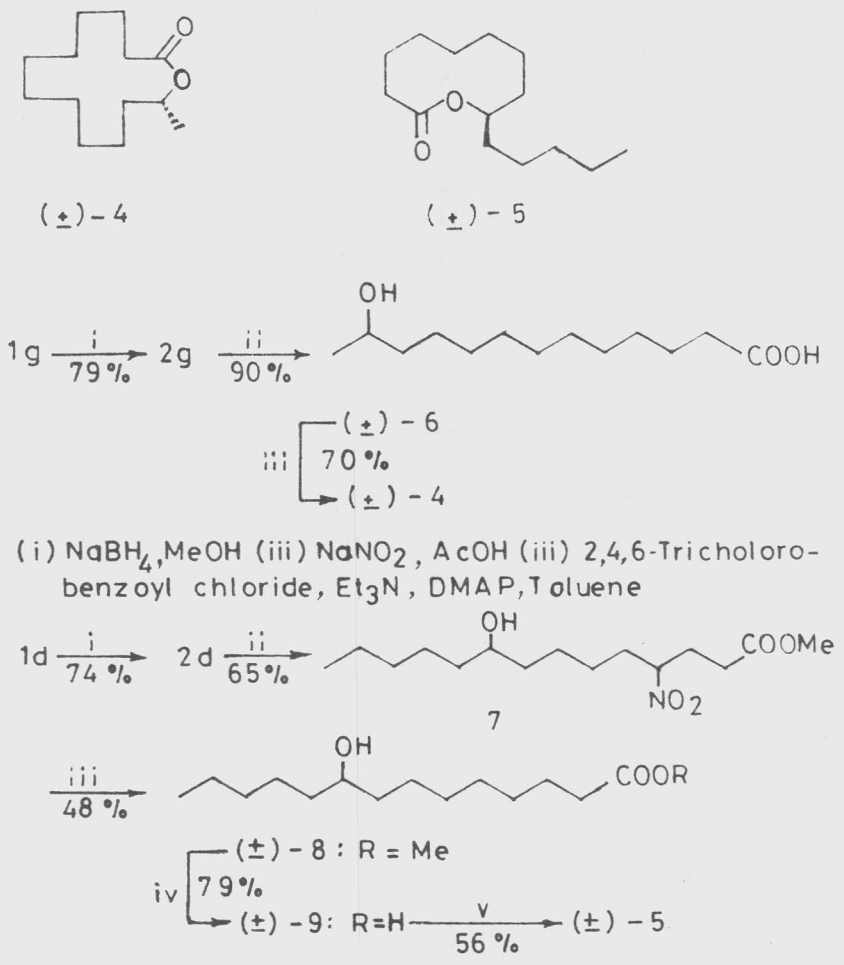
It may be noted that such type of nitroalcohols are easily convertible to their corresponding carboxylic acid derivatives by Nef reaction and the resulting long chain carboxylic acids with a hydroxy function in a remote position are important precursors for a wide variety of bioactive natural products viz. macrolides, aromacroponents etc. and are synthesised via multistep procedures. We have demonstrated the utility of our procedure by achieving short syntheses of (±)-tridecanolide[11] **4** and (±)-9-tetradecanolide[12] **5** (Scheme II).

Compound **1g** was prepared by treating 2 equivalents of methyl magnesium bromide in Et_2O with 1 equivalent of 2-nitrocyclohexanone at RT as per procedure described by Ballini *et al.*[5]. Compound **1g** on treatment with $NaBH_4$ in dry MeOH as per procedure given in the experimental



1,2	R	n	% Yield of 2a-g
a	Me	1	85
b	Et	1	89
c	Pr	1	89
d	Amyl	1	74
e	Ph	1	70
f	Vinyl	1	33 (50)
g	Me	7	79

Scheme I



Scheme II

gave nitroalcohol (±)-**2g** in 79 % yield. Treatment of (±)-**2g** with $NaNO_2$ and acetic acid in *N,N*-dimethyl sulfoxide[13] gave (±)-12-hydroxytridecanoic acid **6** in 90% yield, which on subsequent macrolactonisation following literature procedure[14] gave macrolide (±)-**4** in 70 % yield.

In a similar fashion **1d** was converted to **2d** in 77% yield , which on treatment with methyl acrylate in the presence of Amberlyst A-21 resin in the absence of a solvent gave the adduct **7** in 65% yield as a gum. Denitration of **7** and subsequent hydrolysis to **9** have been achieved by treating **7** successively with AIBN and tributyltinhydride in refluxing benzene and LiOH in THF-water system. Macrolactonization of **9** to (±)-9 tetradecanolide **5** has been achieved following the literature procedure[14].

Experimental Section

^{1}H NMR spectra were recorded in $CDCl_3$ at 60 MHz unless otherwise stated using TMS as the internal standard (chemical shifts are expressed in δ, ppm). IR spectra were recorded as thin films unless otherwise stated. All chemicals were purified before use and literature methods were followed for the synthesis of 2-nitrocyclohexanones[15] and *tert*-2-nitroalcohols[5].

1-Amyl-2-nitrocyclohexanol 1d : Yield 74% (oil); IR ($CHCl_3$): 3450 (OH), 1540 cm^{-1}; ^{1}H NMR:

0.65 (t, J=6Hz, 3H, $-CH_3$), 0.9-1.6 (br, 16H, $-CH_2-$), 2.6 (br, 1H, OH), 4.2 (dd, J=10 and 4 Hz, 1H, $-CHNO_2$) (Found: C, 60.97 ; H, 9.97 ; N, 6.45. Calc. for $C_{11}H_{21}NO_3$: C, 61.37 ; H, 9.83 , N, 6.51%).

1-Methyl-2-nitracyclododecanol 1g: Yield 64%; IR ($CHCl_3$) : 3450, 1540 cm^{-1}; ^1H NMR: 1.0 (s, 3H, $-CH_3$), 1.1-1.6 (br, 16H, $-CH_2-$), 1.8-2.1 (br, 4H, $-CH_2-$), 4.2 (t, J=7Hz, 1H, $-CHNO_2$) (Found: C, 64.52; H, 10.85; N, 5.48. Calc. for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76 %).

Cleavage of *tert*-Nitroalkanols catalysed by $NaBH_4$: General procedure. To a solution of *tert*-2-nitroalcohol (1 equiv.) in dry MeOH (4 mL/100 mg) was added $NaBH_4$ (1 equiv.) portionwise at r.t.with stirring. When TLC of the reaction mixture showed disappearance of the starting material, the reaction was diluted with H_2O and acidified with 2 *N* HCl and extracted with dichloromethane. After evaporation of the solvent the crude products were purified by chromatography.

7-Nitroheptan-2-ol 2a: Yield 85% (oil); IR (neat) : 3400, 1550 cm^{-1}; ^1H NMR :1.3 (d, J=7Hz, 3H, $-CH_3$), 1.5 (m, 6H, $-CH_2-$), 3.6 (m, 1H, -CH-OH), 4.2 (t, J=6.5 Hz, 2H, $-CH_2NO_2$) (Found: C, 52.45 ; H, 9.72 ; N, 8.72. Calc. for $C_7H_{15}NO_3$; C, 52.16 ; H, 9.38 ; N, 8.69%).

8-Nitrooctan-3-ol 2b: Yield 89%, (oil); IR (neat): 3400, 1550 cm^{-1}; ^1H NMR :1.8 (t, J=6.5Hz, 3H,-CH_3), 1.5 (m, 10H, $-CH_2-$), 3.4 (m, 1H, -CH-OH), 4.2 (t, J=6.5 Hz, 2H, $-CH_2NO_2$) (Found: C, 54.75 ; H, 9.82; N, 7.67. Calc. for $C_8H_{17}NO_3$; C, 54.84 ; H, 9.78 ; N, 7.99%)

9-Nitrononan-4-ol 2c: Yield 89% (oil); IR (neat) : 3450, 1550 cm^{-1}; ^1H NMR :0.9 (t, J=7Hz, 3H, $-CH_3$), 1.5 (m, 12H, $-CH_2-$), 3.5 (m, 1H, -CH-OH), 4.3 (t, J=6.5 Hz, 2H, $-CH_2NO_2$) (Found: C, 57.43; H, 10.25; N, 7.52 . Calc. for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40%).

2-Nitro-1-pentyl-cyclohexan-1-ol 2d: Yield 77% (oil); IR (neat) : 3375, 1540 cm^{-1} ; ^1H NMR : 0.7 (t, J = 5.5 Hz, 3H, $-CH_3$), 0.85-1.5 (m, 16H, - CH_2-), 1.5-1.9 (m, 1H), 3.2 (br, 1H, OH), 4.0 (t. J = 6.5 Hz, 2H, $-CH_2NO_2$) (Found: C, 60.87; H, 10.52; N, 6.62. Calc. for $C_{11}H_{23}NO_3$; C, 60.80; H, 10.67; N, 6.45%).

6-Nitro-1-phenylhexan-1-ol 2e: Yield 70%, (gum); IR (neat) : 3400, 1540 cm^{-1}; ^1H NMR :1.3 (br, 8H, -CH_2), 3.2 (br, 1H, OH), 4.1 (t, J=6.5 Hz, 2H, $-CH_2NO_2$), 4.3 (t, J=6Hz, 1H, -CHOH) (Found: C, 64.62; H, 7.56; N, 6.35. Calc. for $C_{12}H_{17}NO_3$; C, 64.55; H, 7.67; N, 6.27%).

6-Nitro-1-vinylhexanol, 2f: Yield 33%, (oil); IR (neat) : 3400, 1550 cm^{-1}; ^1H NMR: 1.4 (m, 8H, -CH_2-), 3.3 (m, 1H, -CHOH), 4.2 (t, J=6.5 Hz, 2H,-CH_2-NO_2), 5.0-5.5 (m, J=3 Hz, 3H, $-CH=CH_2$) (Found: C, 55.52; H, 8.67; N, 8.27. Calc. for $C_8H_{15}NO_3$; C, 55.47; H, 8.73; N, 8.09%).

13-Nitrotridecan-2-ol 2g: Yield 79% , m.p. 127°; IR (neat) : 3400, 1540 cm^{-1} ; ^1H NMR :1.3 (d, J=6.5 Hz, 3H, $-CH_3$), 1.5-1.6 (br, 20H, - CH_2-), 3.7 (m, 1H, -CH-OH), 4.3 (t, J=6.5 Hz, 2H, $-CH_2NO_2$) (Found: C, 63.75; H, 11.27; N, 5.85. Calc. for $C_{13}H_{27}NO_3$; C, 63.64; H, 11.09; N, 5.71%).

Synthesis of (±)-12-hydroxytridecanoic acid, (±) 6. A solution of (±)-**2g** (0.120 g, 0.42 mmole) in DMSO (2 mL) was stirred with sodium nitrite (0.09 g, 1.3 mmole) and acetic acid (0.4 mL, 4.2 mmole) at 35°C for 6h. After acidification with a 10% aq. solution of HCl, the product was extracted several times with ethyl acetate, the solvent was removed under reduced pressure and purified by TLC (EtOAc:Hexane, 1:5) giving 0.108 g (90%) of (±)-**6**. IR: 1720 cm^{-1}; ^1H NMR: 0.9-1.4 (br, 21H, $-CH_2-$, $-CH_3$), 1.90 (t, J=5 Hz, 2H, $-COCH_2-$), 3.5 (m, 1H, -CH-OH) (Found: C, 67.85; H, 11.42. Calc. for $C_{13}H_{26}O_3$; C, 67.79; H, 11.38%).

Macrolactonization of (±)-6 and synthesis of (±)-4. (±)-12-Hydroxytridecanoic acid (0.08g, 0.35 mmole) in anhyd. THF (10 mL) under argon was treated with 2,4,6- trichlorobenzoyl chloride (0.13g, 0.46 mmole) and anhyd. Et_3N (0.05g, 0.47 mmole). The mixture was stirred overnight and filtered through celite. The filtrate was diluted with anhydr. toluene (200 mL) and the solution was added to a refluxing solution of *N, N*-dimethylaminopyridine (DMAP, 0.024g, 0.2 mmole) in anhyd. toluene (100 mL). After refluxing for 3h the mixture was concentrated and the residue was washed successively with 0.5 *N* HCl, $NaHCO_3$ and brine and dried (Na_2SO_4). Evaporation and column

chromatography using 10% ethyl acetate in hexane yielded 0.052g, (70 %) of (±)-**4** as an oil. IR: 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.20 (d, *J*=6.5 Hz, 3H, $-CH_3$), 1.25-1.5 (m, 14H, $-CH_2-$), 1.60-1.75 (m, 4H, $-CH_2-$), 2.20-2.50 (m, 2H, $-COCH_2-$), 4.9 (m, 1H, -O-CH-) (Found: C, 73.82; H, 11.54. Calc. for $C_{13}H_{24}O_2$; C, 73.54; H, 11.39%).

Reaction of (±)-2d with methyl acrylate: A solution of (±)-**2d** (0.71 g, 2.74 mmole) in CH_2Cl_2 (0.5 mL) and methyl acrylate (0.25 mL, 2.74 mmole) was mixed with Amberlyst A-21 resin (1 g) and stirred for overnight at r.t. The resin was then washed with CH_2Cl_2 and the washings were evaporated to yield a residue which was purified by chromatography (10% acetone in toluene) to give 0.52 g (65%) of **7** as gum; IR ($CHCl_3$) : 1730, 1550 cm^{-1}; ^1H NMR: 0.8 (t, *J*=6Hz, 3H, $-CH_3$), 0.9-1.45 (m, 16H, $-CH_2-$), 2.1 (t, *J*=5Hz, 2H, $-CH-COOCH_3$), 1.82 (s, 3H, $-OCOCH_3$), 3.5 (s, 3H, $COOCH_3$), 3.7 (m, 1H, CH-OH)4.5 (m, 2H, $-CH-NO_2$) (Found: C, 59.42; H, 9.75; N, 4.59. Calc. for $C_{15}H_{29}NO_5$; C, 59.38; H, 9.63; N, 4.62 %).

Preparation of (±) methyl 9-hydroxy-tetradecanoate (±)-8. A solution of 7 (0.35 g, 1.15 mmole) in anhyd. benzene (5 mL), tributyltin hydride (0.4 mL, 1.5 mmole) and AIBN (0.01 g) were mixed and refluxed under nitrogen atmosphere for 2 h while monitoring the reaction by TLC. The mixture was evaporated under reduced pressure and the residue washed with aq. $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. Further purification of this residue by column chromatography using 10% acetone in toluene as eluent gave (±)- **8** (0.14 g , 48%) as gum; IR ($CHCl_3$): 1730 cm^{-1}; ^1H NMR : 0.8 (t, *J*=6 Hz, 3H, $-CH_3$), 0.9-1.5 (m, 20H, $-CH_2-$), 2.1 (t, *J*=6 Hz, 2H, $-CH_2-COOCH_3$), 3.5 (s, 3H, $-COOCH_3$), 2.8 (br, 1H, -CH-OH) (Found: C, 69.85; H, 11.63. Calc. for $C_{15}H_{30}O_3$; C, 69.72; H, 11.70%).

Preparation of (±)-9-hydroxytetradecanoic acid, (±)-8. (±)-Methyl-9-hydroxytetradecanoate (0.25 g, 0.97 mmole) was dissolved in THF (10 mL) and to this were added water (10 mL) and LiOH (0.146 g, 6.35 mmole) and the mixture was stirred at r.t. for 15 h. When the reaction was completed the mixture was acidified with 2*N* HCl (2×10mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by purification on column chromatography gave 0.19g (79%) of the product (±)-**9** as gum. IR: 1720 cm^{-1}; ^1H NMR: 0.35 (t, *J*=6.5 Hz, 3H, $-CH_3$), 0.85 (br, 20H, $-CH_2-$), 1.97 (t, 2H, *J*=5 Hz, $-CH_2-COOH$), ; 3.5 (m, 1H, -CH-OH) (Found: C, 68.87 ; H, 11.72. Calc. for $C_{14}H_{28}O_3$; C, 68.81; H, 11.55%).

Macrolactonization of (±)-8. (±)-9-Hydroxytetradecanoic acid (0.17 g, 0.696 mmole) in anhyd. THF (10 mL) under argon was treated with 2,4,6-trichlorobenzoyl chloride (0.24 g, 0.97 mmole) and anhyd. Et_3N (0.1 g, 0.97 mmole). The mixture was stirred overnight and filtered through celite. The filtrate was diluted with anhyd. toluene (200 mL) and the solution was added to a refluxing solution of *N, N*-dimethylaminopyridine (DMAP, 0.5 g, 4 mmole) in anhyd. toluene (100 mL). After refluxing for 3h the mixture was concentrated and the residue was washed with 0.5 *N* HCl, $NaHCO_3$ and brine and dried (Na_2SO_4). Evaporation and column chromatography using 10% ethyl acetate in hexane yielded 0.08g (56%) of (±)-**5** . IR: 1720 , 1245 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): 0.9(t, *J*=6.8 Hz, 3H, $-CH_3$), 1.0-1.61 (m, 16H, $-CH_2-$), 2.18 (m, 2H), 2.50 (m, 1H), 4.89 (m, 1H, -CH-O-$COCH_2$) (Found: C, 74.42; H, 11.82. Calc. for $C_{14}H_{26}O_2$; C, 74.29; H, 11.58%).

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References

1 Seebach D , Colvin E W , Lehr F & Weller T, *Chimia*, **1979,** 33; Varma R S & Kabalka G W, *Heterocycles*, 24, **1986,** 2645; Rajappa S, *Tetrahedron*, 37, **1981,** 1453; Barrett A G M & Graboski G G, *Chem Rev*, 86, **1986,** 751; Yoshikoshi A & Miyashita M, *Acc Chem Res*, 18,, **1985,** 284; Seebach A & Knochel P, *Helv Chim Acta*, 67, **1984** 261. Roshini, G, Ballini, R & Marotta, E, *Tetrahedron*, 45 **1989**, 5935; Ballini R & Bosica G, *Synthesis*, **1994**, 723

2 Hassner A , Larkin J M & Dowd J E *J Org Chem*, 33, **1968,** 1733.

3 Ballini R & Petrini M, *Synth Commun*, 16, **1986,** 1781; Matlak A S & Breslow D S, *J Org Chem*, 32, **1967,** 1995; Aono T , Bieri J H , Hesse M, Kostova K , Lorenzi- Riatsch A , Nakashita Y & Prewo R, *Helv Chim Acta*, **1985,**

1037 and references cited therein; Southwich P L , Fitzerald J A , Madhav R & Welsh D A, *J Org Chem,* **34, 1969,** 3279.

4 Stach H & Hasse M, *Tetrahedron,* **44, 1988,** 1573; Nikon A & Silversmith E F , *Organic Chem: The Name Game Modern Coined Terms and Their Origin,* (Pergamon Press New York NY), **1987,** 257.

5 Ballini R , Bartoli G , Garriboldi P V , Marcantoni E & Petrini M, *J Org Chem,* 58, **1993,** 3368.

6 Saikia A K , Hazarika M J, Barua N C , Bezbarua M.(S). Sharma R P & Ghosh A C *Synthesis,* **1996,** 981.

7 Bezbarua M S , Saikia A K , Barua N C , Kalita D & Ghosh A C, *Synthesis,* **1996,** 1289.

8 Ballini R , Petrini M & Rosini G, *Tetrahedron,* 46, **1990,** 7531.

9 Ballini R & Palestini C, *Tetrahedron Lett,* 35, **1994,** 5731.

10 Dampawan P & Zajac (Jr) W, *Tetrahedron Lett,* **1982,** 135.

11 Bestmann H J & Kellermann W, *Synthesis,* **1994,** 1257.

12 Bollbuck B , Kraft P & Tochtermann W, *Tetrahedron,* 52, **1996,** 4581.

13 Matt C , Wagner A & Micoskowski C, *J Org Chem,* 62, **1997,** 234.

14 Inanaga J , Hirata K , Saeki H , Katsuki T & Yamaguchi M, *Bull Chem Soc Jpn,* 52, **1979,** 1989.

15 Ozbal H & Zajac (Jr.) W.W, *J Org Chem,* 46, **1981,** 3082.