Tetrahedron Vol. 43, No. 22, pp. 5315 to 5320, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

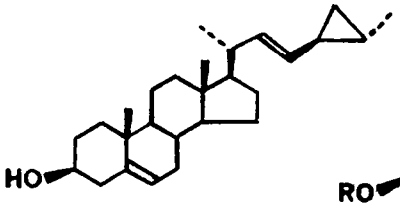
STEREOSELECTIVE SYNTHESIS OF SIDE CHAIN OF GLAUCASTEROL USING PALLADIUM (0) CATALYST.

J.P. GENET* and J.M. GAUDIN
Laboratoire de Chimie Organique et Organométallique
Associé au C.N.R.S.
Université Pierre et Marie Curie - 8, rue Cuvier - 75005 - Paris-FRANCE

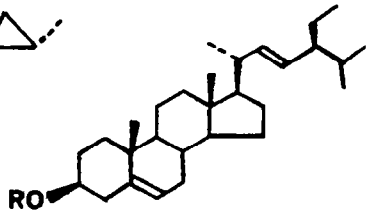
(*Received in Belgium 7 September* 1987)

Abstract : A stereoselective synthesis of glaucasterol **1** with vinylic cyclopropane on the side chain, has been developed using palladium (0) catalyst and gave complete chirality transfer from C_{22} of benzoate **15** to C_{24} of glaucasterol **1**.

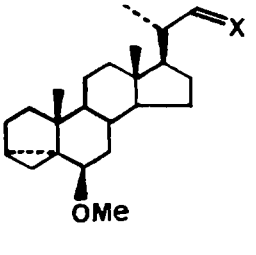
The unique feature of marine sterols such as glaucasterol **1** is the novel side chain with a vinylic cyclopropane moiety.[1] Since recent isolation (from the soft coral Sarcophyton glaucum[2], deep sea gorgonians[3]) and structural determination [4], two partial syntheses[3,4] of glaucasterol have been reported.[5] This motivated us to look for the elaboration of the unusual side chain of glaucasterol in connection with our work on synthesis of vinylic cyclopropanes of biological interest[6] and our recent synthesis of chiral dictyopterene (A).[7] The abundant plant sterol stigmasterol **2** is an attractive starting material for the synthesis of the aldehyde **5**. The three steps of the sequence **2** ⟶ **5** (i.e. the protection of 3β - hydroxy - Δ^5 system **2** into the 3α, 5α cyclo-6β methoxy derivatives **4**) are classical. Accordingly, stigmasterol was converted into the tosylate **3** followed by methanolysis in the presence of potassium acetate[8] and ozonolysis of the protected stigmasterol **4**.[9] We have now used the building block **5** for a stereoselective synthesis of glaucasterol **1** as shown in scheme 2.

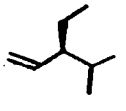


1

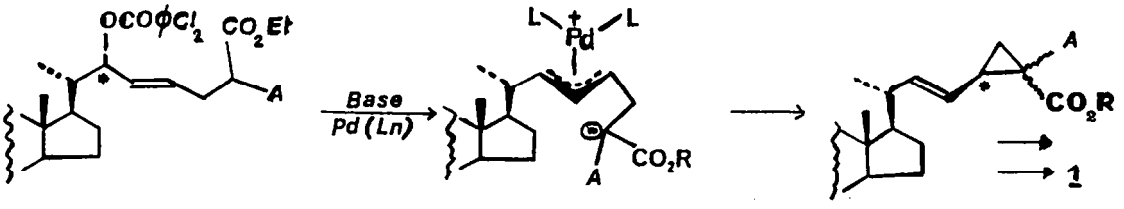


2 R = H
3 R = Ts



4 X = 
5 X = O

The key reaction was based on the promoted cyclisation of chiral allylic compounds such as **6**, which was effected by a double inversion according scheme 1. The process allows a net SYN, S_EN' substitution of the benzoate by the C-C bond in the cyclopropane **8**,[10] via cationic n^3 allyl species **7**.

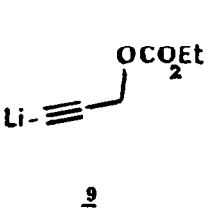


6 7 8

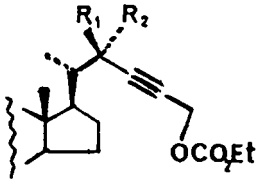
Scheme 1

The desired allylic functionalized derivatives 14, 15 were obtained in a four steps sequence. The aldehyde 5 was treated with the lithio acetylide 9[11] in THF at -78°C to give a 6 : 4 epimeric mixture of the 22 alcohols (60% yield) separable by flash chromatography over silica gel : the major less polar isomer (22 R) 10[12] ; mp = 103-104° $(\alpha)_D^{20}$ = + 42° (C=3.05 $CHCl_3$), and the more polar minor isomer (22 S) 11[12], oil $(\alpha)_D^{20}$=+38.5° (C=2.95 $CHCl_3$).

Semi-hydrogenation of the requisite (22 S) derivative 11 with Lindlar catalyst afforded the Z - allylic alcohol 12 (97% yield). Subsequent alkylation with ethyl p.toluene sulfonyl acetate and Pd $(dppe)_2$ 7% (THF/ 25°C/1h) gave 13 (76% yield) which was then converted into the corresponding carbonate 14 (70% yield) using EtOCOCl/pyridine (CH_2Cl_2/25°C/1h) or benzoate 15 (89% yield) with 2,4-dichlorobenzoyl chloride/ pyridine (CH_2Cl_2 /25°C/1h).

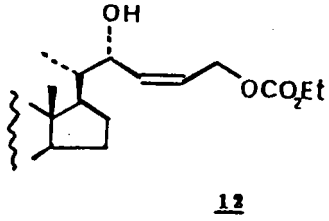


9

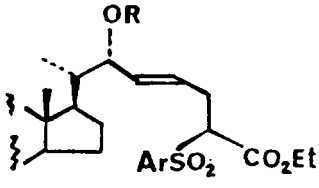


10 R_1 = OH , R_2 = H

11 R_1 = H , R_2 = OH

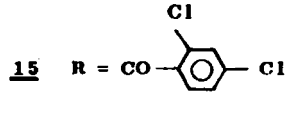


12

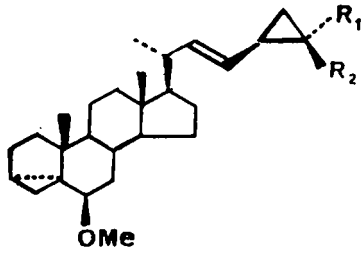


13 R = H

14 R = CO_2Et



15



16 R_1 = CO_2Et, R_2 = SO_2-Me

17 R_2 = CO_2Et, R_1 = SO_2-Me

18 R_1 = CO_2tBu, R_2 = H

19 R_1 = CH_2OH, R_2 = H

20 R_1 = CH_3 R_2 = H

Scheme 2

Surprisingly palladium catalyst failed to promote cyclisation of carbonate 14.[13] In sharp contrast, the intramolecular ScN' catalyzed reaction with 8% Pd (dppe)$_2$ of the 2-4 dichlorobenzoate 15 was achieved under very mild conditions : (DBU/10 min/25°C) giving 16 and 17 (90% yield), with exclusive E stereochemistry of the double bond of the vinylic side chain.
These compounds were converted into the trans alcohol by treatment with Na (Hg)/ Na_2HPO_4 in methanol, tBuOK in benzene and finally $LiAlH_4$ in THF, giving a single product 19.[14] The transfer of the chirality from C_{22} to C_{24} was highly stereoselective via the η^3 allyl species (scheme 1). There is apparently no racemisation[15] in the step 15 ⟶ 16, 17, the η^3 allyl species 7 (A=SO_2Ph ; L=dppe) gave high degree of chirality transfer with the 2,4-dichlorobenzoate as leaving group. The allylic carbonate 14 did not react in our case.

The final transformation of the alcohol 19 into glaucasterol was performed as previously reported [4,16] : treatment of 19 with $MeSO_2Cl$ / Et_3N in pyridine and then $LiAlH_4$ in ether (0°C) followed by acidic hydrolysis of 20 (p.TsOH, dioxane, H_2O) gave the glaucasterol 1 m.p. 112-114°C, litt.[4,3a] 112-113°C and 108-110°C. ^1H NMR data (500 MHz, $CDCl_3$) and mass spectra were identical with those previously reported.[2,3]

EXPERIMENTAL

GENERAL

All reactions were carried out under argon. "Usual work up" means pouring the reaction mixture into water, extracting with ether or CH_2Cl_2, washing the combined organic layers with water, drying with solid $MgSO_4$ and removing the solvent in vacuo using a rotatory evaporator. Flash column chromatography was carried out on SiO_2 (Merck or S.D.S Kieselgel 230-400 Mesh). T.L.C were carried out on Merck SiO_2 plates. Melting points (m.p.) were determined on a Kofler hot stage and are uncorrected, IR. Spectra (max in cm^{-1}) were recorded on Perkin-Elmer 297 spectrophotometer. Proton magnetic resonance spectra (^1H-NMR) were recorded at 80, 250 and 500 MHz on Brucker WP 80, A.M 250 and 500 spectrometers respectively. Chemical shifts are reported in ppm (standard TMS ppm = 0) with the notation giving the numbers of protons, according to the usual numbering of steroïds the multiplicity of the signals and the coupling constants (if applicable) ; spin multiplicily is given by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Brucker AM 250 MHz Chemicals shifts (C) are quoted in ppm and are referenced to $CDCl_3$. 1,2-bis (diphenylphosphino) ethane, (dppe), was purchased from Aldrich Chemical Co., Pd (dppe)$_2$ was prepared using published procedure[17] and handled under argon. Optical rotations were measured using a Perkin Elmer 241 automatic polarimeter. Microanalyses were performed by the laboratory of University Pierre and Marie Curie.

(20S)-6 β -methoxy-3 α ,5 β -cyclo-20-pregnane carboxaldehyde 5 :

Compound 5 was prepared from stigmasterol 2 in 70% overall yield, according to the procedure of Steele and Mosettig[8] in 70% overall yield from stigmasterol 2. R_f = 0.39 eluent ACOEt/Hexane 1 : 9. IR (film) 2960, 2880, 1740. ^1H-NMR, 2.75 (m, H-C(6)) ; 3.25 (s, O-CH_3) ; 10.3 (H-CO).

Reaction of 5 with lithioacetylide 9 :

A THF solution of 9 (from the corresponding carbonate 15g, 12 mmol and 1 eq of LDA) was cooled at -78°C and 5 was added dropwise. After 5 min. the reaction mixture was partitioned in water-ether and furnished after usual work up the alcohols 10 and 11 (60%) in a ratio 6:4 which were separated by flash chromatography (ether/hexane 4 : 6) 11 (oil) ; $(\alpha)_D^{20}$=+ 38.5° (C=2.95, $CHCl_3$) ; IR (film) : 3450, 3060, 2950, 1750. and 10 m.p. 103-104°C ; $(\alpha)_D^{20}$ = + 42° (C = 3.05, $CHCl_3$). IR : 3450, 3060, 2950, 1750.

Synthesis of 12 :

A methanol solution (0.5 M) of 11 2.42g (5 mmol) were stirred over 0.060g of Pd Lindlar catalyst[18] under 1 atmosphere of H_2. After absorption of 1 eq of hydrogen, filtration of catalyst and evaporation of methanol, 12 was obtained as a yellow oil $(\alpha)_D^{20}$= 21.5° (=3.65 $CHCl_3$) IR (film) : 3500, 2950, 1735, 1470, 1260. ^{1}H-NMR (250MHz) ($CDCl_3$).0.42(m,H-C(3));0.64(t,J=2Hz,H_2-C-4));0.99(d,H_3-C(21));1.00(s,H_3-C(19));4.53(dd, J=8.2Hz and J=3.7Hz, H-C(22)) ; 4.63 (1H, dd,J=12.7 and J=5.1Hz =-CH_2-O-) ; 4.69 (1H, dd,J=12.7 and 7.4 Hz -=-CH_2-O-) ; 5.78 (2H, m, -CH=CH). Found : C,74.30 ; H,10.20. Calc. for $C_{29}H_{46}O_5$; C,73.70 ; H,9.7.

Ethyl(4E)(6R)-6-hydroxy-6-(20S-6β-methoxy-3,α5α-cyclopregnanyl)-2-paratoluene sulfonyl-4-hexenoate 13 :

A mixture of 12 (4.74g 10 mmol) in dry THF (40ml) (5.13g,14 mmol) of ethyl paratoluene sulfonyl acetate, 0.630g (7%) of Pd (dppe)$_2$ was stirred at 25°C. After 1hr usual work up, the chromatography (ether/hexane 55:45) funished 13 (4.76g 76%) m.p 85-88°C.
IR (film) 3500, 2950, 1730, 1600. ^{1}H-NMR 500MHz ($CDCl_3$) : 0.43(m,H-C(3)) ; 0.65(t,J=2Hz, H_2-C(4)) ; 0.72(s,H_3-C(18)) ; 1.00(s H_3-C(19)) ; 1.17(t=7.7Hz, CH_2CH_3) ; 2.69 and 2.79(m, CH_2-C(25)) ; 2.77(br.s,-C(6)) ; 3.32(s,CH_3O-) ; 3.97(m, H-C (26) ; 4.10(q,J=7.2Hz, CH_2-CH_3) ; 5.54(m,-CH=CH-) ; 7.35(d,J=1.5Hz) ; 7.75 (d,J=1.5Hz). Found : C,69.98 ; H,8.86 ; S,5.0, Calc. for $C_{37}H_{54}O_6S$: C,70.89 ; H,8.68 ; S,5.12.

(4E) (6R)-6-(dichloro 2,4-phenylcarbonyloxy)-6-(20 S-6-paratoluenesulfonyl-4-hexenoate 15 :

To a solution of (3.76g, 6 mmol) of 13 were added 2 eq of pyridine and 1.2 eq of 2-4 dichlorobenzoylchloride. The mixture was stirred 1hr. then treated with HCl 5% and washed with water. After usual work-up and chromatography separation (ether/hexane 55 :45) 4.27g (89%) of 15 was obtained $(\alpha)_D^{20}$ = 42.1° (C=3 $CHCl_3$).IR (film) 2960, 2870, 1730, 1585, 1450 ^{1}H-NMR ($CDCl_3$) 500 MHz. 0.43 (m, H-C(3)) ; 0.64(t,J=2.5Hz H_2-C(4)) ; 0.72(s,H_3-C(18)) ; 1.00(s, H_3C(19)) ; 2.77(br.s, H-C(6) ; 3.32(H_3O-) ; 2.69 and 2.80 (m H_2-C(25)) ; 3.96(m, H-C(26)) ; 5.46(m,C(24)=CH-) ; 5.65(m,-HC=C(23). Found : C,66.80 ; H,6.44 ; S,4.72. Calc. for $C_{44}H_{56}O_7Cl_2$; C,66.07 ; H,7.06 ; S,4.01 ; Cl,8.86.

Synthesis of 16 and 17 :

A solution of 15 (4g,5 mmol) in dry THF (20ml), 0.315g (7%) of Pd (dppe)$_2$ and 1.4 eq (7.6g) of D.B.U was stirred at room temperature. Work up and chromatography (ether/hexane 45 : 55) gave 2.68g (88%) of 16 and 17 $(\alpha)_D^{20}$ = + 25.9° (C = 3.15 $CHCl_3$). IR (film) : 2940, 2870, 1730, 1600, 1450, 1370. ^{1}H-NMR 250 MHz ($CDCl_3$). 0.44 (m, H-C(3)) ; 0.65 (br.s, H-C(4)) ; 0.65 (s,H_3C(18)) ; 0.97 (d,J=7Hz, CH_3-C(21)) 1.00 (s, H_3 C(19)) ; 1.12 (t,J=7.5Hz, CH_2-CH_3); 3.32 (CH_3-O) ; 5.08 (dd,J=7.5 and 15Hz (C23)) ; 5.63 (dd,HC=C(22)=CH,J=7.5 and 15Hz) ; 7.38 (2H) and 7.8 (2H). Found : C,72.05 ; H,8.4 ; S,5.2. Calc. for $C_{37}H_{52}O_5S$; C,71.89 ; H,8.04 ; S,5.4.

(E)-(1S,2S)2-6(β-Methoxy-3α,5α cyclo-20 (s) pregnanyl) vinyl cyclopropane methanol 19 :

A solution of (1.4g 2.30 mmol) of 16 and 17 in dry methanol (0,1M) was added 5 eq of Na_2HPO_4 followed by 5 eq. of Na(Hg) 6%. The stirring was continued for 2h at RT to give after work up the crude ester which was dissolved in a benzene solution of t.BuOK (0.1 M) 1.5 eq and refluxed 6h. benzene was evaporated and the crude product was partitioned in ether-water. The ether solution was washed with aqueous 2N hydrochloric acid, dried over $MgSO_4$ and evaporated to yield a mixture of ethyl and t.Butyl esters with 18 as the major product). This mixture was dissolved in ether (0.1M) and the solution treated at room temperature by $LiAlH_4$ (2 eq). After 10 min. the reaction mixture was treated with a saturated solution of sodium sulfate and filtered. Evaporation of ether gave after chromatography (ethyl acetate/hexane 1 : 2) ; 0.530 mg (56%) of 19 for the three step sequence : desulfonylation, epimerisation and reduction.

IR (film) 3400, 3060, 2940, 2870, 1450, 1380.$(\alpha)_D^{20}$=45.1 (C=3 $CHCl_3$) ; ^{1}H-NMR (500 MHz) ($CDCl_3$) ; 0.43 (m,H-C(3)) ; 0.58 (m,H_2C-(26)) ; 0.65 (t,J=2Hz, H_2C-(4)) ; 0.72 (s, H_3 C-(18)) ; 1.00 (d, J=6Hz, H_3 C-(21)) ; 1.02 (s, H_3 C-(19)) ;2.77(br.s,H-C-(6)) ; 3.32 (s,CH_3O) ; 3.45 and 3.51 (m, $-CH_2$-OH) ; 4.95(dd,-CH=C(23), J=15 and 8Hz) ; 5.35(dd,(22)C=CH, J=15 and 8Hz) M.S : m e 70 eV M^+ : 412(20), 397(10), 380(25), 363(10), 357(35) ; 253(65) ; 159 (30) ; 145(35) ; 121(30) ; 105(60) ; 91(70) ; 81(100). Found : C,81.5 ; H,10.6. Calc. for $C_{28}H_{44}O_2$; C,80.06 ; H,10.27.

(E) (1S,2S)-2(methoxy-6 β-cyclo-3α-5α) 20S pregnanyl-2-vinyl-1-methyl cyclopropane 20 :

To a solution of 19 (0,225g 0.546 mmol) in dichloromethane (5ml) were added at 0°C 0.155 ml of triethylamine,and 0.085 ml of methanesulfonylchloride. The stirring was continued for 20 mn at 0°C. The reaction mixture was poured in cold HCl aqueous solution (0.5 N). The organic layer was separated and washed with cold water Usual work up gave the crude mesylate, which was immediately dissolved in dry THF (5ml). This mixture was added dropwise to a stirred and cold solution of $LiAlH_4$ (0.170g) in 5ml of THF. The stirred solution was allowed to come at 40°C for 40 mn. After usual work up and chromatography (EtOAc/Hexane 1 : 49) gave 20 (0.180g,83%) $(\alpha)_D^{20}$ = +49° (c = 4.35 $CHCl_3$) ^{1}H-NMR ($CHCl_3$) 80 MHz 2.77 (br. s, H-C(6)) ; 3.25 (s, CH_3O) ; 5 (m, 2H,-CH=CH-). Found : C,85.08 ; H, 11.02. Calc. for $C_{28}H_{44}O$; C,84.85 ; H, 11.5.

Glaucasterol 1:

To a solution of 0.100g (0.252 mmol) of 20 in dioxanne (3ml) and water (0.8ml) was added one cristal of PTSA. The mixture was heated for 2h at 90°C and allowed to come at room temperature and then 5ml of water were added. The white solide was collected by filtration.

Recristallisation from hexane gave 0.084g (87%) of glaucaterol 1. m.p. 112-114° ; $(\alpha)_D^{20}$ = - 37.8° (C = 0.86 $CHCl_3$). ^{1}H-NMR data, 500 MHz ($CDCl_3$) 0.678 (s, H_3-C(18)) ;0.992 (d,J=6.3 Hz, H_3C(21)) ; 1.005 (H_3C(25)) ; 1.038 (d,J=6 Hz, H_3-C(27)) ; 4.898 (dd,J=8.6 and 15 Hz, = CH-C(23)) ; 5.284 (dd,J=8.5 and 15 Hz CH-C-(22)) ; 5.35 (m,He-(6).M.S (70 ev) : m/e, M^+ : 367 (30) ; 358 (40) ; 300 (10) ; 271 (20) ; 159 (25) ; 145 (20) ; 109 (100) ; 93 (40) ; 81 (75) ; 67 (70) ; 55 (75). Found : C,84.49 ; H,10.65. Calc. for $C_{27}H_{42}O$; C, 84.82 ; H, 10.99.

ACKNOWLEDGMENT. Help of Ministère de la Recherche et de la Technologie (MRT) is gratefully acknowleged for a grant to J.M.G (1984-1986).

Reference and notes

1) Review C. Djerassi, N. Theobald, W.M.C. Kokke, C.S. Pak and R.M.K. Carlson, Pure Appl.Chem., 51 1815 (1979).

2) M. Kobayashi and H. Mitsuhasi, Steroids 40, 665 (1982).

3) a) C. Bonini, R.B. Kinnel, M. Li, P.J. Scheuer and C. Djerassi, Tetrahedron Letters, 24, 277 (1983) ; b) C.A.N. Catalan and C. Djerassi, Tetrahedron Letters, 24 3461 (1983).

4) Y. Fujimoto, M. Kimura, T. Terasawa, F.A.M. Khalifa and N. Ikekawa, Tetrahedron Letters, 25, 1805 (1984).

5) For recent synthesis and isolation of other marine sterols containing cyclopropane ring in the side chain a) R. D. Walkup, G.D. Anderson and C. Djerassi, Tetrahedron Letters, 767 (1979) ; b) Y. Fujimoto, M. Okhava, T. Terasawa and N. Ikekawa , Tetrahedron Letters, 26, 3239 (1985). For general reviews in connection of the side chain elaboration a) D.M. Piatak and J. Wicha, Chem.Rev., 78, 199 (1978) ; b) J. Redpath and F.J. Zeelen, Chem.Soc.Rev., 12, 75 (1983).

6) a) J.P. Genêt, F. Piau and J. Ficini, Tetrahedron Letters, 21, 3183 (1980) ; b) J.P. Genêt and F. Piau, J.Org.Chem., 26, 2414 (1981) ; c) J.P. Genêt, M. Balabane and F. Charbonnier, Tetrahedron Letters, 23, 5027 (1982) ; d) A. Denis, J.P.Genêt and F. Charbonnier, Bull.Soc.France, 793 (1986).

7) F. Colobert and J.P. Genêt, Tetrahedron Letters, 26, 2779 (1985).

8) J.A. Steele and E. Mosettig, J.Org.Chem., 28, 571 (1963).

9) W.G. Salmond and M.C. Sobala, Tetrahedron Letters, 1695 (1977).

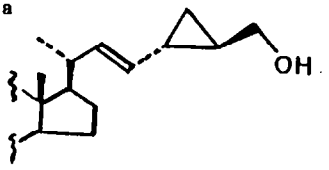
10) For other examples of chirality transfer using palladium complexes see 7 and 13b and references cited therein.

11) The lithium acetylide 9 was obtained by deprotonation of the corresponding acetylenic carbonate by slow addition of LDA at -78°C in THF.

12) The configuration at C-22 of 10 and 11 were established by conversion into known acetylenic alcohols (ref.4).

13) For an excellent recent review see ; a) Organopalladium compounds in organic synthesis B.M. Trost and T.R. Veerhoeven ; Comprehensive Organometallic Chemistry, Ed G. Wilkinson Pergamon Press (1982) ; b) For a more recent but partial review see: J. Tsuji, Tetrahedron, 42, 4011 (1986).

14) 10 gave the alcohol 21 via the same sequence described above (24R, 25R) $(\alpha)_D^{20}$ = 16° (c=1.48 in $CHCl_3$), m.p. = 112-114°C, ^{1}H-NMR (500 Mhz in $CHCl_3$) 5.32 (22-H) ; 1.24 (24-H) ; 4.96 (23-H)., which is the precursor of the minor (24R, 25R) natural sterol component of papakusterol.[3a]



21 24 (R) , 25 (S)

15) For a partial discussion of chirality transfer and the merit of allylic carbonate in such reactions (which did not reac in our case) see 13b p.4280.

16).We are gratefull to Professor N.Ikekawa and Dr. Y. Fujimoto,for providing us the experimental details for this sequence.

17) D.R. Coulson, Inorg. Synth., 13, 121 (1972) see also Y.S. Varshavskji and N.V. Kiseleva, Chem. Abstract, 80, 122897v (1974).