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SODIUM BIS(2-METHOXYETHOXY)(1,1,1,3,3,3-HEXAFLUORO-2-PROPOXY)ALUMINUM HYDRIDE, A NEW STEREOSELECTIVE REDUCING AGENT IN A CARBACYCLIN SYNTHESIS

Susumu Harashima[a], Osamu Oda[a], Shigeo Amemiya[b] and Koichi Kojima*[b]
Process Development Laboratories[a] and Medicinal Chemistry Research Laboratories[b]
Sankyo Co.,Ltd., 2-58, Hiromachi 1-Chome,Sinagawa-ku,Tokyo,140 Japan.

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ABSTRACT: A new reducing agent (**2j**) reduced the enone (**4**) to give 15(*S*)-allylic alcohol (**5a**) with excellent regio- and stereoselectivity through a five membered ring transition state. Stereoselectivity of this reaction will be explained based on the LUMO of the enone moiety. The resulting (**5a**) was led to a carbacyclin.

Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH)[1] (**1**) is a useful reducing agent because of both its high solubility in hydrocarbon solvents or tetrahydrofuran and its higher stability in air than other reducing agents. Modification of SMEAH with one molar equivalent of simple alcohols, such as methanol, was reported to give a reducing agent that had a stable structure in contrast to lithium trialkoxyaluminum hydride.[2] This modified SMEAH reagent has been reported to reduce simple ketones or halogen-containing hydrocarbons, at room temperature or higher, to give the corresponding alcohols or hydrocarbons.[2,3] However, no report has been published on reduction of the enone moiety with this reagent.

We have been interested in reduction of an enone, especially carbacyclin 15-enone[4] (PG numbering) such as (**4**) to 15(*S*)-allylic alcohol (**5a**), by SMEAH modified with various alcohols (**2a-j**)(Fig. 1 and Table 1). These reducing agents were easily prepared from achiral, commercially available, and inexpensive materials. In paticular, we focused our attention on 1,2-regioselectivity and 15(*S*)-stereoselectivity, because the generation of 15(*S*)-allylic alcohol moiety as a biologically active substructure is one of the synthetic challenges.[5]

Here, we wish to report that a new reducing agent, sodium bis(2-methoxyethoxy)(1,1,1,3,3,3-hexafluoro-2-propoxy)aluminum hydride (**2j**) reduced, even at low temperature, the carbacyclin 15-enone (**4**) to give 15(*S*)-allylic alcohol (**5a**) stereoselectively, and the resulting 15(*S*)-hydroxy compound (**5a**) was led to a carbacyclin (**14**)[6].

The starting enone (**4**) was prepared by two steps from the alcohol (**3**) through a similar method reported by Kojima *et al.*[7] Reduction of (**4**) with methanol-modified SMEAH reagent, bis(2-methoxyethoxy)(methoxy)aluminum hydride (**2a**), proceeded at -78°C to yield a mixture of the allylic alcohols (**5a,5b**) in good yield. As expected it was found that 1,2-reduction occurred regioselectively with this modified SMEAH reagent. However, compared to the reduction with SMEAH itself, improvement of 15(*S*)-stereoselectivity was not observed as shown in Table 1.

In order to increase the 15(S)-selectivity, we then investigated the reduction of (**4**) in more detail by

modifying SMEAH with various hydroxy-containing compounds. These results are summarized in Table 1. When simple aliphatic alcohols were employed, the degree of stereoselectivity varied with the alcohols used as ligands; slightly better selectivity was obtained with EtOH, *n*-PrOH and *n*-BuOH, but the selectivity did not vary with *i*-PrOH and *t*-BuOH. On the other hand when aliphatic alcohols containing an electron withdrawing group were employed, excellent stereoselectivity was obtained, and especially with sodium bis(2-methoxyethoxy)(1,1,1,3,3,3-hexafluoro-2-propoxy)aluminum hydride (**2j**), the best 15(*S*)-stereoselectivity, 15(*S*)/15(*R*) ratio of 94/6, was achieved[8].

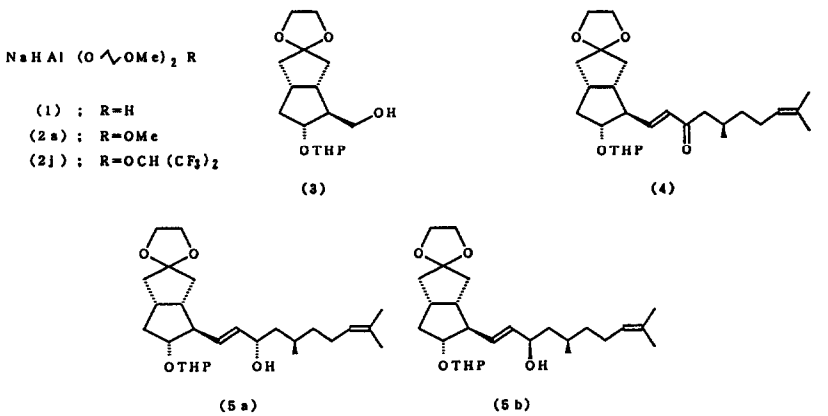

Figure 1

Table 1. Influence of ligands R in aluminum reagent, NaAlH(O⌒OMe)$_2$R, on stereoselectivity in the reduction of the enone (4)

Ligand R=	ratio of alcohol 15S (5a) : 15R (5b)
(1) H	77 : 23
(2a) MeO	77 : 23
(2b) EtO	84 : 16
(2c) ^{n}-PrO	83 : 17
(2d) ^{i}-PrO	78 : 22
(2e) ^{n}-BuO	82 : 18
(2f) ^{t}-BuO	77 : 23
(2g) MeO⌒O	86 : 14
(2h) FCH_2CH_2O	83 : 17
(2i) F_3CCH_2O	89 : 11
(2j) $(F_3C)_2CHO$	94 : 6

All reactions were carried out in THF at −78 °C.

Furthermore, as shown in Tables 2 and 3, the ratio of the 15(*S*)-alcohols increased by lowering the reaction temperature, and tetrahydrofuran or diethyl ether was the solvent of choice. From these results, it was found that sodium bis(2-methoxyethoxy)(1,1,1,3,3,3-hexafluoro-2-propoxy)aluminum hydride (**2j**) had a strong reducing power, even at low temperature(-78°C), and was an excellent reducing agent for control of the stereochemistry in the reduction of carbacyclin 15-enone (**4**). Thus, we could obtain the 15(*S*)-allylic alcohol (**5a**)[9] in good yield after chromatographic purification.

Table 2. Effect of the temperature on the stereoselectivity in the reduction of the enone (4) with the reagent (2j)

Temp.	ratio of alcohol 15S (5a) : 15R (5b)
-46°C	90 : 10
-66°C	92 : 8
-78°C	94 : 6

All reactions were carried out in THF.

Table 3. Effect of the solvent on the stereoselectivity in the reduction of the enone (4) with the reagent (2j)

Solv.	ratio of alcohol 15S (5a) : 15R (5b)
MeO∿OMe	88 : 12
	92 : 8
Et_2O	94 : 6
THF	94 : 6

All reactions were carried out at -78°C.

This high 15(*S*)-selectivity is explained based on transition states (**Ia,Ib,Ic** and **Id**) coupled with the consideration of electronic factors (Fig. 2); a conformation of the five membered ring in (**4**) is considered to be fixed by the OTHP substituent at C_{11} and the ω-side chain at C_{12}, both of which would take quasi-equatorial positions. The C_{12}-H bond and the C_{13} double bond are considered to be synperiplanar according to the allylic strain concept[10]. Thus, the reducing agent approaches from the less hindered side of the carbonyl group regardless of the conformation (s-*cis* or s-*trans*) of the enone moiety[11] (Fig. 3)(for the sake of clarity only the s-*cis* conformation is depicted). We also consider that the reduction of a carbonyl group with sodium bis(2-methoxyethoxy)(1,1,1,3,3,3-hexafluoro-2-propoxy) aluminum hydride (**2j**) is initiated by complexation of sodium ion to an oxygen atom, which activates the carbonyl group.[12]

On the other hand, it is quite reasonable to assume that aluminum reagent (**2j**) exists mainly in two types of enantiomeric conformers such as (**IIa**) and (**IIb**) (Fig. 4).[13] In this conformation, sodium ion is fixed in the center of the four oxygen atoms by complexation of the oxygen lone-pair electrons, and two methylene groups of the 2-methoxyethoxy group exist in gauche conformation. The structure of (**2j**) indicates clearly that it exists in a contact ion pair[12], and we also hypothesize that the reduction proceeds through a cyclic transition state in which five atoms, including the oxygen, the carbon, the hydrogen, the aluminum and the sodium, are in the same plane (Fig. 5)[14].

Accordingly, when the reduction proceeds, four types of transition states, e.g. (**Ia**),(**Ib**),(**Ic**) and (**Id**), are conceivable based on s-*cis* and s-*trans* conformation for the enone moiety (Fig. 2). Among these, (**Ia**) is the most plausible transition structure because, in this particular case, a favorable n-π^* attractive orbital interaction between the LUMO of the enone moiety and the oxygen nonbonded orbital of (**2j**) is observed.

In this case, an n-π repulsive orbital interaction between the oxygen and the double bond, which presumably gives rise to an undesirable 15(*R*)-hydroxy product, will be surmounted by n-π^* attractive orbital interaction.[15] Therefore, the reduction proceeds through the transition state (**Ia**) to yield 15(*S*)-

hydroxy epimer stereoselectively. It is also noted that the 15(*S*)-stereoselectivity goes up with the number of fluorine atom introduced into the alkoxy group of the aluminum reagent as shown in Table 1. The introduction of an electron withdrawing fluorine atom into an alkoxy group of the reducing agent decreases the reducing ability. Accordingly, a closer contact of the aluminum reagent with the enone moiety is required as a reduction occurs. This means a more favorable n-π^* orbital interaction is strengthened by the introduction of a fluorine atom. Hence, higher 15(*S*)-hydroxy selectivity is attributed to the stronger n-π^* orbital interaction induced by a fluorine atom, and the highest 15(*S*)-selectivity was obtained with (**2j**) containing six fluorine atoms.

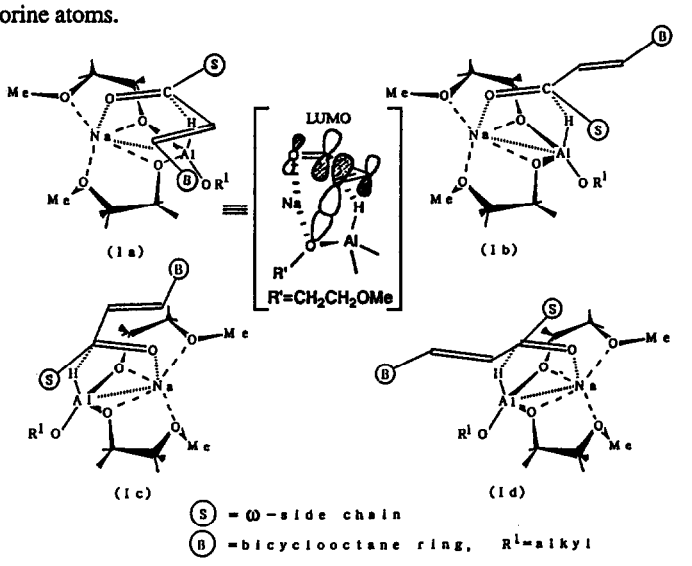

Figure 2

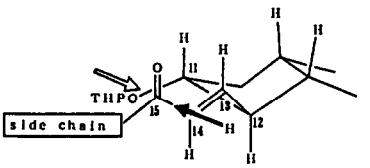

Figure 3

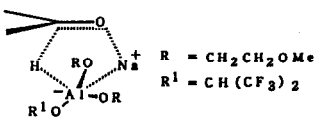

Figure 5

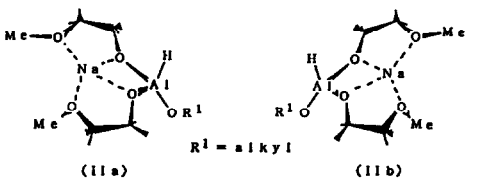

Figure 4

Next, the alcohol (**5a**) was converted to a carbacyclin (**14**) by the following methods. Deprotec-

tion of (5a) with hydrochloric acid gave the diol (6), which was treated with dihydropyran and *p*-toluenesulfonic acid to yield the ketone (7). The Wittig reaction of (7) in DMSO with the ylide, derived from triphenyl 4-carboxybutylphosphonium bromide, afforded the more polar (5*E*)-acid (8a) together with the less polar (5*Z*)-acid (8b) [(8a)/(8b) ratio of 2 to 1]. The stereochemistry at the C_5 position was assigned based on the following evidence: esterification of (8a) and (8b) with diazomethane gave respectively the esters (9a) and (9b). Oxidation of (9a) and (9b) with osmium tetraoxide and sodium metaperiodate, followed by reduction with sodium borohydride, yielded the hydroxy-esters (10a) and (10b). During these reactions, a fairly large amount of the alcohol (11) was formed via a cleavage of the C_5 olefinic linkage. Hydrolysis of (10a) and (10b) with aqueous potassium hydroxide afforded the corresponding hydroxy-acids (12a) and (12b). Lactonization of (12b) with 2,2'-dipyridyldisulfide and triphenylphosphine yielded a macrocyclic lactone (13), which was hydrolyzed to the starting hydroxy-acid (12b) in good yield. In contrast, a similar treatment of (12a) did not give any lactonized material. From these results, the more polar acid (8a) was assigned as (5*E*)-compound and the less polar one (8b) as (5*Z*)-compound. Thus the stereochemistries at the C_5 position in (8a), (8b) and (14) have been unambiguously established . Finally, treatment of (8a) with acetic acid in aqueous tetrahydrofuran afforded the acid(14).

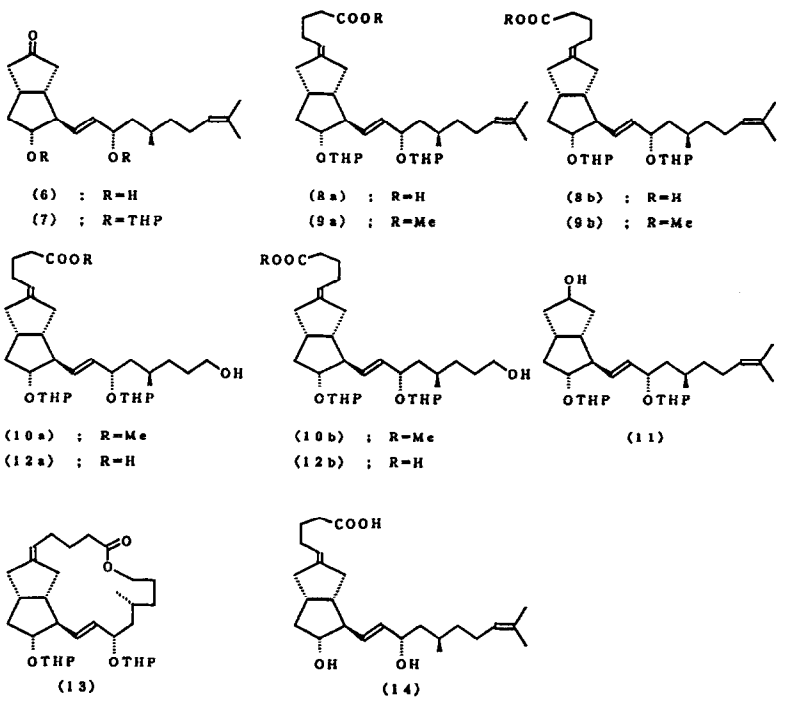

Figure 6

In conclusion, a new highly stereoselective reducing agent (2j) was developed, and its usefulness was shown in a carbacyclin synthesis.

Experimental

IR spectra were recorded on a Jasco IRA-2 spectrometer. ^{1}H-NMR spectra were determined on a Varian T-60 spectrometer, and signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Mass spectra were performed on a JEOL JMS-OLSG spectrometer. Optical rotations were measured with a Perking Elmer model 141 polarimeter. Removal of solvent *in vacuo* was accomplished with a rotating flash evaporator at 20-30 mmHg, usually at 35-50°C. For TLC analysis, precoated silica gel plates (E.Merck 60 F_{254}, 0.25mm) were used and spots were visualized by spraying a solution of 0.5% vanillin in 20% ethanol in sulfuric acid (v/v), followed by heating. Columns for ordinary chromatography were prepared with silica gel (Kanto Chemical Co. Inc., 60-110 mesh) or alumina (E.Merck GII-III). HPLC analysis was carried out on a HITACHI 655 Liquid Chromatograph apparatus with a TOHSOH RI-8000 RI detector, and two different silica gel columns joined in series were used (SENSHU SCIENTIFIC Co., SSC-Silica-292 and SSC-Silica-16).

Preparation of Sodium Bis(2-methoxyethoxy)(1,1,1,3,3,3-hexafluoro-2-propoxy)aluminum Hydride (2j)

To sodium bis(2-methoxyethoxy)aluminum hydride in toluene solution (70 w/w%, 1.09g, 3.76mmol) was added dry THF(50ml) at 25°C under nitrogen atmosphere. To this solution 1,1,1,3,3,3-hexafluoro-2-propanol (574mg, 3.42mmol) in dry THF (4ml) was added dropwise at the same temperature. During this operation, approximately 1 eq. of hydrogen gas was evolved. The reaction mixture was stirred at room temperature for 20min. A 20ml portion of the solution of this reagent was collected and the removal of the solvent *in vacuo* gave 690mg of (**2j**) as a viscous colorless oil. IR(neat) : 2840,1770,1215,855cm^{-1}. (Absorption of 3400 and 900 cm^{-1} caused by 1,1,1,3,3,3-hexafluoro-2-propanol, and 1680 and 765cm^{-1} caused by SMEAH disappeared.)

(1*S*,2*R*,3*R*,5*R*)-2-[3-Oxo-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane (4)

Dry THF (130ml) was added to 930mg of 55% sodium hydride (17.5 mmol in mineral oil, washed with hexane). 6.2g (22.4 mmol) of dimethyl 2-oxo-4(*R*),8-dimethyl-7-nonenyl phosphonate was added to this suspension at room temperature, and then 5.19g (17.5 mmol) of (1*S*,2*R*,3*R*,5*R*)-2-hydroxymethyl-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane [7] in dry THF(10 ml) was added with ice-cooling. After being stirrerd for 2hr the reaction mixture was neutralized by acetic acid, and THF was evaporated *in vacuo*. This mixture was dissolved in hexane (50ml) and washed with water, 5% aqueous NaOH , water, 1% aqueous HCl, 5% aqueous $NaHCO_3$ and water successively, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 7.57g of an oily residue. This was purified by neutral alumina (GII) column chromatography. Elution with 2% AcOEt in hexane (v/v) gave 6.52g (83%) of the enone (**4**) as a colorless oil. IR(neat): 1692,1670,1625,1035,982cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.92(3H,d,*J*=6Hz), 1.08(3H,s,CH_3), 1.61(3H,s,CH_3), 3.90(4H,s,-CH_2CH_2-), 5.10(1H,brt,=CH-), 6.18-7.0(2H,m,-CH=CH-). MS: *m/z* 362(M^+-84),344,318. $[\alpha]_D^{23}$+16.0°(c=1.2,MeOH).

(1*S*,2*R*,3*R*,5*R*)-2-[3(*S*)-Hydroxy-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane (5a) and (1*S*,2*R*,3*R*,5*R*)-2-[3(*R*)-Hydroxy-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-3-(tetrahydropyran-2-yl)oxy-7,7-ethylenedioxybicyclo[3.3.0]octane (5b)

Sodium bis(2-methoxyethoxy)aluminum hydride in toluene solution (70 w/w%, 210mg, 0.726mmol) was diluted with dry THF(10ml) and then 1,1,1,3,3,3-hexafluoro-2-propanol (111mg, 0.660mmol) in dry THF (1ml) was added dropwise at 25°C. After being stirrerd for 20min the whole was cooled to -78°C and the enone (**4**) (148mg, 0.33mmol) in dry THF (1ml) was added. After being stirrerd at the same temperature for 2.5hr the reaction mixture was quenched with 0.3ml of 5 w/w% aqueous sodium hydroxide, diluted with 5ml of brine at ambient temperature, and extracted with AcOEt (20ml). The organic layer was washed with brine twice, dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 156mg of a crude oil. The HPLC analysis of this oil showed 94:6 [(**5a**):(**5b**)] ratio of the alcohols. This was purified by silica gel column chromatography (10g). Elution with 20-22% AcOEt in hexane (v/v) gave 131mg(88%) of 15(*S*)-alcohol (**5a**) and further elution with 24-30% AcOEt in hexane (v/v) gave 9mg(6%) of 15(*R*)-alcohol (**5b**).

(**5a**) ; IR(neat):3480,2930,2860,1120,1030cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.92(3H,d,*J*=6Hz,CH_3), 1.60(3H,s,CH_3), 1.67(3H,s,CH_3), 3.88(4H,s,OCH_2CH_2O), 4.67(1H,m,O-C<u>H</u>-O), 5.08(1H,brt,*J*=7Hz, =CH-), 5.52(2H,m,olefinic-H). MS : *m/z* 346(M^+-102). $[\alpha]_D^{23}$+1.2°(c=1.0,$CHCl_3$). HPLC:t_R 7.4 and 7.6min (two diastereomers based on THP group): mobile phase; a 2:5 mixture of ethyl acetate and hexane, flow rate; 6 ml/min.

(**5b**) ; IR(neat): 3430,2935,2880,1130,1020cm^{-1}. ^{1}H-NMR($CDCl_3$)δ: 0.90(3H,d,*J*=6Hz,CH_3), 1.60(3H, s, CH_3), 1.68(3H, s, CH_3), 3.89(4H, s, OCH_2CH_2O), 4.64(1H, m, O-C<u>H</u>-O), 5.09(1H, brt, *J*=7Hz, =CH-), 5.58(2H, m, olefinic-H). MS: *m/z* 346(M^+-102). $[\alpha]_D^{23}$+10.9°(c=1.0,$CHCl_3$). HPLC:t_R 12.1min [Two diastereomers based on THP group were not separated in the same condition as for (**5a**).]

General procedure for reduction of the enone (4)

Reduction of (**4**) with SMEAH or reagents (**2a-i**) in toluene, Et_2O or DME was performed in a similar manner to that of (**5a**) by changing the ligand alcohols or the solvents. 15(*S*)/15(*R*) Ratio was determined by HPLC analysis of the products.

(1*S*,2*R*,3*R*,5*R*)-2-[3(*S*)-Hydroxy-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-7-oxobicyclo[3.3.0]octan-3-ol (6)

3.3% Hydrochloric acid (40ml) was added dropwise to a solution of the compound (**5a**) (4.05g) in acetone (40ml) and the resulting mixture was stirred for 30min at 0°C and 1hr at room temperature. Stirring at room temperature was continued for 2 hr, during which time additional water (20ml) was added. The reaction mixture was diluted and extracted with AcOEt, washed with aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 55% AcOEt in hexane (v/v) and AcOEt afforded (**6**) (2.64g,91%). IR(neat): 3400,1740,970cm^{-1}. ^{1}H-NMR($CDCl_3$) δ : 0.91(3H,d,*J*=6Hz,CH_3), 1.60(3H,s,CH_3), 1.67(3H,s,CH_3), 3.6-4.4(2H,m,C<u>H</u>OH x2), 5.02(1H,brt,*J*=7Hz,=CH-), 5.50(2H,m,olefinic-H). MS: *m/z* 302(M^+-18),284. $[\alpha]_D^{23}$-13.0°(c=1.0, MeOH).

(1*S*,2*R*,3*R*,5*R*)2-[3(*S*)-(Tetrahydropyran-2-yl)oxy-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-3-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octan-7-one (7)

A mixture of the alcohol (**6**) (2.64g,8.24mmol), dihydropyran (2.25ml) and a catalytic amount of p-TsOH in CH_2Cl_2 (40ml) was stirred under ice-cooling for 30min. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by neutral alumina (GII) column chromatography. Elution with 20-30% Et_2O in hexane (v/v) afforded (**7**) (4.12g,quant.) as a colorless oil. IR (neat):1740,1033,1020cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 4.66(2H,brs,O-C$\underset{|}{}$H-O x2), 4.9-5.7(3H,m,olefinic-H). MS: *m/z* 404(M^+-84),386,302,254. $[\alpha]_D^{23}$-34.3° (c=1.0, $CHCl_3$).

17(*R*)-Methyl-20-isopropylidenecarbacyclin 11,15-Bis(tetrahydropyran-2-yl) Ether (8a) and (5*Z*)-17(*R*)-Methyl-20-isopropylidenecarbacyclin 11,15-Bis(tetrahydropyran-2-yl) Ether (8b)

(4-Carboxybutyl)triphenylphosphonium bromide (4.8g) was added to a solution of sodium metyl sulfinylmethide [prepared from 55% NaH in oil (720mg) and DMSO (40ml) in the usual manner] at 15-20°C. After being stirrerd for 30min, the resulting red-colored solution was treated with the ketone (**7**) (190mg,0.379mmol) in DMSO (2ml). The reaction mixture was stirred at room temperature overnight, then poured into ice water, acidified with conc.HCl (1ml), and extracted with cyclohexane. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 10-15% AcOEt in hexane (v/v) afforded the (5*Z*)-compound (**8b**) (27mg,12%) as a colorless oil, and then elution with 15-30% AcoEt in hexane (v/v) afforded the (5*E*)-compound (**8a**) (55mg,25%) as a colorless oil.

(**8a**) ; IR(neat): 2930,1740,1708,1020,975cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93(3H,m,CH_3), 1.61(3H,s,CH_3), 1.68(3H,s,CH_3), 4.73(2H,brs,O-C$\underset{|}{}$H-O x2), 5.0-5.75(4H,m,=CH- x4). MS : *m/z* 470(M^+-102),386,370. $[\alpha]_D^{23}$+13.6°(c=1.0,$CHCl_3$).

(**8b**) ; IR(neat): 2930,1739,1708,1020,974cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.93(3H,m,CH_3), 1.61(3H,s,CH_3), 1.67(3H,s,CH_3), 4.73(2H,brs,O-C$\underset{|}{}$H-O x2), 5.0-5.75(4H,m,=CH- x4). MS : *m/z* 470(M^+-102),386,370. $[\alpha]_D^{23}$-2.6°(c=1.0,$CHCl_3$).

17(*R*)-Methyl-20-isopropylidenecarbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl) Ether (9a)

Treatment of (**8a**) (113mg,0.197mmol) in Et_2O (5ml) with excess diazomethane in Et_2O followed by evaporation of the solvent and purification with silica gel column chromatography (1g) with 30% AcOEt in hexane (v/v) afforded 104mg(90%) of (**9a**) as an oil. IR(neat): 1733,1039,1025cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,m,CH_3), 3.67(3H,s,CH_3), 4.70(2H,brs,O-C$\underset{|}{}$H-O), 5.0-5.8(4H,m,CH=CH,=CH- x2). MS: *m/z* 484(M^+-102),466.

(5*Z*)-17(*R*)-Methyl-20-isopropylidenecarbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl) Ether (9b)

Esterification of (**8b**) (124mg,0.216mmol) and then treatment as described for the esterification of (**8a**) afforded 111mg(87%) of (**9b**) as an oil. IR(neat) : 1732,1039,1025cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,m,CH_3), 4.70(2H,brs,O-C$\underset{|}{}$H-O), 5.0-5.8(4H,m,CH=CH,=CH- x2). MS : *m/z* 484(M^+-102),466.

(5*Z*)-17(*R*)-Methyl-20-hydroxycarbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl) Ether (10b) and (1*S*,2*R*,3*R*,5*R*)-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-5(*R*),9-dimethyl-1(*E*),8-decardienyl]-3-(tetrahydropyran-2-yl)oxy-7-hydroxybicyclo[3,3,0]octane (11)

Osmium tetraoxide (100mg) and sodium metaperiodate (3.0g) were added to a mixture of the ester (**9b**) in dioxane (30ml) and water (10ml). The whole was stirred at room temperature for 2.5hr. The reaction mixture was diluted with brine and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (60g). Elution with 5-10% AcOEt in hexane (v/v) afforded 2.12g of the starting material, and further elution with 20-30% AcOEt in hexane (v/v) gave 322mg of crude products. The products in EtOH (5ml) were reduced with $NaBH_4$ (47mg) under ice-cooling. After being stirrerd for 15min, excess reagent was decomposed with AcOH, and the reaction mixture was diluted with brine and then extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel chromatography (20g). Elution with 20-30% AcOEt in hexane (v/v) afforded 104mg of (**10b**), and then elution with 40-50% AcOEt in hexane (v/v) gave 103mg of the alcohol (**11**).

(**10b**) ; IR(neat) : 3470,1740,1035,1022cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.94(3H,brd,CH_3), 3.61(3H,s,CH_3), 4.73(2H,brs,$_{O\text{-}\underset{|}{C}H\text{-}O}$), 5.0-5.7(3H,m,$CH_3$). MS *m/z*: 460($M^+$-102),442,416.

(**11**) ; IR(neat) : 3470,1025cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.92(3H,m,CH_3), 4.72 (2H,brs,$_{O\text{-}\underset{|}{C}H\text{-}O}$), 5.0-5.8 (2H,m,CH=CH). MS ; *m/z* : 304(M^+-196),286(M^+-204).

17(*R*)-Methyl-20-hydroxycarbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl) Ether (10a)

Osmium tetraoxide (30mg) and sodium metaperiodate (1.0g) were added to the ester (**9a**) (1.27g) in a mixture of dioxane (90ml) and water (30ml). The whole was stirred at room temperature for 5hr. Treatment and reduction with $NaBH_4$ as described for the synthesis of (**10b**) gave 62mg of (**10a**) as an oil. IR(neat):3480,1740,1040,1022cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H,brd,CH_3), 3.62 (3H,s,CH_3), 4.64 (2H,brs,$_{O\text{-}\underset{|}{C}H\text{-}O}$), 4.90-5.8 (3H,m,CH=CH,=CH-). MS *m/z*:460(M^+-102),442,416.

(5*Z*)-17(*R*)-Methyl-20-hydroxycarbacyclin 11,15-Bis(tetrahydropyran-2-yl) Ether (12b)

A mixture of the alcohol(**10b**) (100mg) and 5% KOH in 30% H_2O-MeOH (10ml) was stirred at room temperature for 2hr. The reaction mixture was acidified with AcOH, diluted with brine and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (5g). Elution with AcOEt gave 89mg(73%) of the acid (**12b**). IR(neat): 3380,1735,1710,1035,1022cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,brd,CH_3), 4.76(2H,brs,$_{O\text{-}\underset{|}{C}H\text{-}O}$), 5.0-5.7(3H,m,CH=CH,=CH-). MS *m/z*: 446(M^+-102),428,402,362. $[\alpha]_D^{23}$ -16.7°(c=1.0, $CHCl_3$).

17(*R*)-Methyl-20-hydroxycarbacyclin 11,15-Bis(tetrahydropyran-2-yl) Ether (12a)

A mixture of the alcohol(**10a**) (60mg) and 5% KOH in 30% H_2O-MeOH (10ml) was stirred at room temperature for 1hr. Treatment as described for (**12b**) afforded 49mg(67%) of (**12a**) as an oil. IR(neat):

3400,1730,1710,1038,1022cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,brd,CH_3), 4.75(2H,brs,O-C H-O), 5.0-5.7(3H,s,CH=CH,=CH-). MS *m/z*: 446(M^+-102),428,402,362. $[\alpha]_D^{23}$ +2.0° (c=1.0,$CHCl_3$).

(5*Z*)-17(*R*)-Methyl-20-hydroxycarbacyclin 11,15-Bis(tetrahydropyran-2-yl) Ether 1,20-Lactone (13)

Triphenylphosphine (61mg) and then 2,2-dipyridyldisulfide (51mg) were added to a solution of the acid (**12b**) (85mg) in toluene (70ml). The whole was heated at 80°C for 4hr. Additional triphenylphosphine (30mg) and 2,2-dipyridyldisulfide (25mg) were added, and heating was continued for 3 hr. A small amount of AcOEt was added to the reaction mixture, and the whole was washed with 1% aqueous NaOH solution, brine, 2% aqueous AcOH and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was purified by silica gel column chromatography (10g). Elution with 7-10% AcOEt in hexane (v/v) gave 21mg of a crude product, which was further purified by thin layer plate [silica gel, 2mm x1, 23% AcOEt in hexane (v/v)] yielding 8mg(10%) of the lactone (**13**). IR(neat): 1732,1035,1021cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,m,CH_3), 4.73(2H,brs,O-C H-O), 5.1-5.8(3H,m,CH=CH,=CH-). MS *m/z* : 530(M^+),428,344 $[\alpha]_D^{23}$+43.3°(c=1.0, $CHCl_3$).

The hydrolysis of the lactone (13)

A mixture of (**13**) (3mg) and 5% KOH in 30% H_2O-MeOH was allowed to stand at room temperature overnight. The reaction mixture was diluted with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (acid washed, 0.5g). Elution with AcOEt afforded 2mg of (**12b**) as an oil.

Lactonization Reaction of the compound (12a)

Triphenylphosphin (45mg) and then 2,2-dipyridyldisulfide (36mg) were added to a solution of the acid (**12a**) (60mg) in toluene (50mg). The whole was heated at 80°C for 4hr, and then additional triphenylphosphine (23mg) and 2,2-dipyridyldisulfide (13mg) were added and heating was continued 3 more hr. Treatment as described for (**13**) afforded none of the material having an Rf value around the lactone (**13**) on silica gel thin layer chromatogram.

17(*R*)-Methyl-20-isopropylidenecarbacyclin (14)

Water (20ml) was added to a solution of the compound (**8a**) (2.05g,3.58mmol) in a mixture of THF (10ml) and AcOH (10ml). The whole was heated at 50°C for 9hr. During this time additional water (20ml) was added and then the mixture was allowed to stand at room temperature overnight. The reaction mixture was diluted with brine, and extracted with cyclohexane. The extracts were washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 45% EtOAc in hexane (v/v) and EtOAc afforded 1.11g(77%) of (**14**) as a colorless oil. IR (neat): 3350,1710,967cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.92(3H,d,*J*=6Hz,CH_3), 1.61(3H,s,CH_3), 1.68(3H,s,CH_3), 3.93(1H,m,CHOH), 4.40(1H,m,CHOH), 4.9-5.4(2H,m,=CH-,=CH-), 5.48(2H,m, -CH=CH-). $[\alpha]_D^{23}$+63°(c=1.0,$CHCl_3$). MS : *m/z* 386(M^+-18),368.

References and Notes

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2) No disproportionation was reported for SMEAH reagent. Strouf, O. *Collect. Czech. Chem. Commun.* **1971**, 36, 2707.

3) Chapka, M.; Chvalovsky, V. *Collect. Czech. Chem. Commun.* **1969**, 34, 3110.

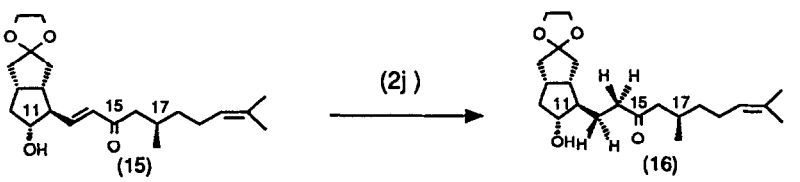
4) The reduction of the carbacyclin enone with chiral (*S*)-BINAL-H was reported to give the 15(*S*)-compound stereoselectively [15(*S*)/15(*R*)=95.9/4.1]; Konishi, Y.; Kawamura, M.; Iguchi,Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, 37, 4391. However, other achiral reducing agents, such as $NaBH_4$, diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide, Corey's trialkylhydroborate prepared from thexylborane and *d,l*-limonen gave rather poor results in 15(*S*)-selectivity (64%,67% and 74% respectively) in the reduction of (4).

5) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chan, C-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, 109, 7925. (b) Kojima, K.; Koyama, k.; Amemiya, S. *Tetrahedron* **1985**, 41, 4449.

6) 17(*R*)-Methyl-20-isopropylidencarbacyclin sodium,(CS-570), was clinically investigated.

7) Kojima, K.; Amemiya, S.; Koyama, K.; Sakai, K. *Chem. Pharm. Bull.* **1985**, 33, 2688.

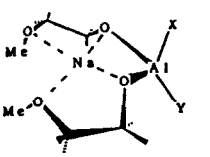
8) Reduction of 17-unsubstituted derivative (PG numbering) of (4) gave a comparable result with a ratio of 15(*S*)/15(*R*)=86/14. In contrast, reduction of the compound having an 11-unprotected hydroxyl group (**15**) proceeded in another way to yield a double bond saturated compound (**16**) as a single product. This shows that the protection of the hydroxyl group at the C_{11} is necessary for 1,2-regioselective reduction of the enones with this new reagent (**2j**).



9) 15(*S*)-configuration of (**5a**) was assigned based on the positive Cotton Effect in the circular dichromism spectrum of its benzoate prepared by reaction with benzoyl chloride in pyridine; Gonella, N. C.; Nakanishi, K.; Martin, U. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, 104, 3775.

10) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, 1, 199. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1841.

11) The infrared spectrum of (**4**) indicates a presence of s-*cis* and s-*trans* conformation.



12) Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, 98, 5524.

13) For the sake of clarity we adopted the nonsolvated monomeric structure for (**2j**), although some solvation and cluster formation may be involved. Other possible conformers (**IIc,IId**) could be less probable for a steric reason.

14) We proposed this model based on molecular model inspection for the transition state.

15) Noyori *et al* proposed a similar n-π^* orbital interaction for unusual stereochemical outcome in the reduction of cyclopentenone with BINAL-H; Noyori, R.; Tomino, I.; Tanino, Y.; Nishizawa, M. *J.*

Am. Chem. Soc. **1984**, 106, 6709. However, we consider that this type of interaction is generally possible, although strong or weak, when a stereochemical requirement between the enone moiety and nonbonded orbital of oxygen is properly fulfilled. The crown ether-type of structure in (**2j**) enables this decisive interaction.

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