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A New and Effective Synthetic Method for the Preparation of the Esters, Peptides, and Lactones Using 3-(5-Nitro-2-oxo-1,2-dihydro-1-pyridyl)-1,2-benzisothiazole 1,1-Dioxide. Synthesis of (±)-(*E*)-8-Dodecen-11-olide, Recifeiolide

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3-(5-Nitro-2-oxo-1,2-dihydro-1-pyridyl)-1,2-benzisothiazole 1,1-dioxide (BID-NPy), readily prepared from 3-chloro-1,2-benzisothiazole 1,1-dioxide and 5-nitro-2-pyridone, proved to be a very useful condensing reagent. A variety of esters, dipeptides, and lactones were obtained in excellent yields. Furthermore, BID-NPy was successfully employed for the lactonization step in a new synthesis of a naturally occurring (±)-(*E*)-8-dodecen-11-olide, recifeiolide.

Saccharin is a commercially available industrial product. Its derivative, 3-chloro-1,2-benzisothiazole 1,1-dioxide (BID-Cl) was found to have reactivities as a condensing reagent and has been utilized in the preparation of some peptides.[1] However, the yields were not so good and BID-Cl was found to be very unstable to moisture and could not be stored for a long time. Therefore, we tried to prepare various saccharin derivatives, which are generally stable crystalline compounds,[2] and found that 3-(5-nitro-2-oxo-1,2-dihydro-1-pyridyl)-1,2-benzisothiazole 1,1-dioxide (BID-NPy) (**1**) was a new condensing reagent for the preparation of esters, peptides, and lactones.

BID-NPy was easily prepared by the reaction of BID-Cl and 5-nitropyridone in dry CH_3CN in the presence of triethylamine (TEA). The structure of **1** was confirmed by elemental analysis. The IR spectrum cleanly showed the presence of the carbonyl group at 1670 cm^{-1}. This compound was quite stable on storage.

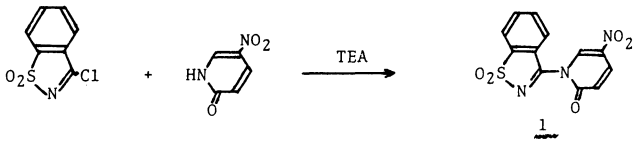

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Table 1. Preparation of esters

BID-NPy + R^1COOH + R^2OH —(Et_3N in CH_2Cl_2, −10 °C to r.t., overnight)→ R^1COOR^2

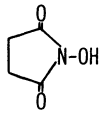
R^1CO_2H	R^2OH	Yield/%	$\nu_{C=O}$/cm^{-1}
$PhCH{=}CHCO_2H$	$PhCH_2OH$	92	1710
$PhCH_2CO_2H$	$PhCH_2OH$	95	1735
$PhCH_2CO_2H$	$O_2NC_6H_4OH$	96	1760
$PhCH_2CO_2H$	CCl_3CH_2OH	93	1760
$PhCO_2H$	$O_2NC_6H_4OH$	88	1735
$PhCO_2H$		93	1765, 1735
$PhCO_2H$	C_6Cl_5OH	93	1745

Table 2. Preparation of protected dipeptide esters

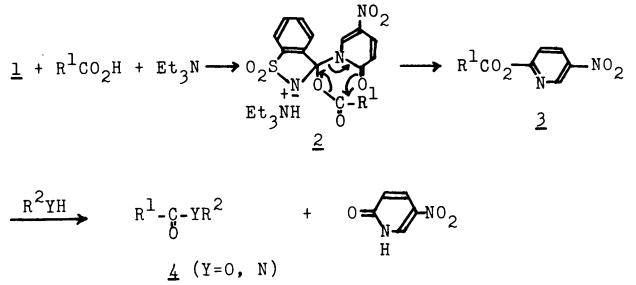
BID-NPy + Y-A.A.-OH[a] + Et_3N —(−10 °C to 0 °C, 2 h, in CH_2Cl_2)→ —(H-A.A-OR, r.t., overnight)→ Y-dipeptid-OR

Product	Yield/%	Mp θ_m/°C(lit)	$[\alpha]_D$/°(*c*, solvent) (lit)	Ref.
Z-Val-Gly-OEt	86	163—164 (162—164)	−27.0 (0.77, EtOH) (−27.0)	12
Z-Ala-Gly-OEt	87	98—99 (99—100)	−21.8 (3.60, EtOH) (−22.2)	12
Z-Met-Gly-OEt	85	94—95 (94—96)	−19.6 (3.50, EtOH) (−19.8)	11
Z-Cys(Bzl)-Gly-OEt	Quant.	97—98 (97—99)	−28.6 (5.86, AcOEt) (−27.0)	11
Boc-Phe-Val-OMe	84	115—117 (118—119)	−11.2 (1.99, DMF) (−11.6)	13
Boc-Leu-Leu-OMe	73	134—135 (132—133)	−50.2 (0.41, MeOH) (−50.4)	14
Boc-Ala-Val-OMe	85	66—67 (63—64)	−49.4 (0.36, MeOH) (−49.5)	15
Boc-Leu-Val-OMe	83	143—145 (144—147)	−41.0 (0.52, MeOH) (−41.1)	16

a) This means *N*-protected amino acids (Y=Z or Boc).

First, **1** was allowed to react with a carboxylic acid in order to check its reactivity. A suspension of equimolar amount of phenylacetic acid, benzyl alcohol, and **1** in dichloromethane was treated with 1 equiv of TEA at −10 °C to room temperature under N_2 to give the expected benzyl phenylacetate in 95% yield. In a similar manner, a variety of esters were obtained in excellent yields, as shown in Table 1. BID-NPy also proved to be an excellent reagent for synthesizing various protected dipeptide esters. The results are shown in Table 2.

The probable course of the reactions of **1** with acids is illustrated in Scheme 1. Formation of the activated ester (**3**, R′= CH_2Ph) could be actually isolated.



Scheme 1.

The preliminary results of ester and amide bond formation with BID-NPy encouraged us to use it to make macrolide. Initially, when TEA was added to a suspension of ω-hydroxy carboxylic acid and **1** (equimolar amount) in dichloromethane at room temperature under N_2 and the reaction mixture was stirred overnight, the yields of the corresponding lactones were not satisfactory. Many attempts to improve the yields under various conditions were unsuccessful. However, when a catalytic amount of *p*-toluenesulfonic acid (TsOH) was added to the reaction mixture, the yield of lactone was increased. Thus, the active ester prepared by the addition of equimolar amount of TEA to a suspension of carboxylic acids **5a—g** and **1** in 1,2-dichloroethane was added dropwise to a refluxing 1,2-dichloroethane containing 2 equiv of TsOH in a period of 6 h using a mechanically driven syringe. The usual work-up of the reaction mixture gave monolides in quite high yields with a small amount of diolides. Such an effect of the acid catalyst seems to be due to the activation of the intermediary active ester, as shown in 7. The results are listed in Table 3.

TABLE 3 LACTONIZATION OF ω-HYDROXY CARBOXYLIC ACIDS

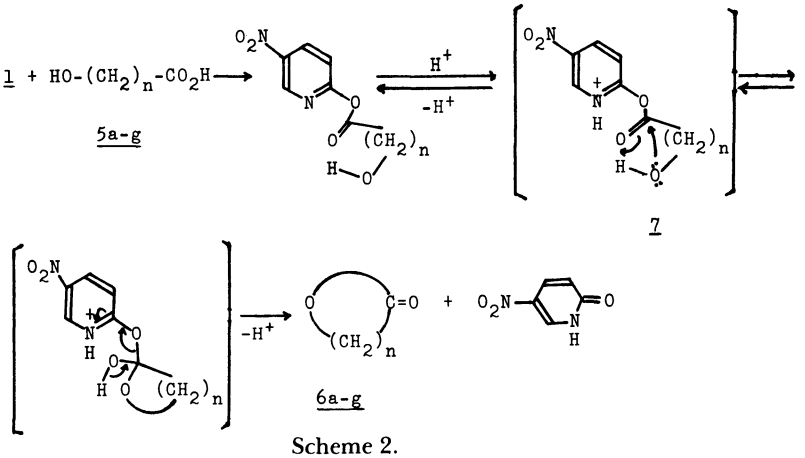
	Hydroxy acids	Lactones(**6a—g**) Ring size	Yield/%
5a	$HO(CH_2)_{10}CO_2H$	12	72
5b	$HO(CH_2)_{11}CO_2H$	13	71
5c	$HO(CH_2)_{12}CO_2H$	14	86
5d	$HO(CH_2)_{14}CO_2H$	16	88
5e	$HO(CH_2)_{15}CO_2H$	17	81
5f	$CH_3(CH_2)_5CH(OH)(CH_2)_{10}CO_2H$	13	86
5g	$CH_3(CH_2)_5CH(OH)CH_2$-Z-$CH{=}CH(CH_2)_7CO_2H$	13	68

The yields of the monolides from ω-hydroxy carboxylic acids (**5a—g**) are comparable to those obtained by any existing methods.[3]

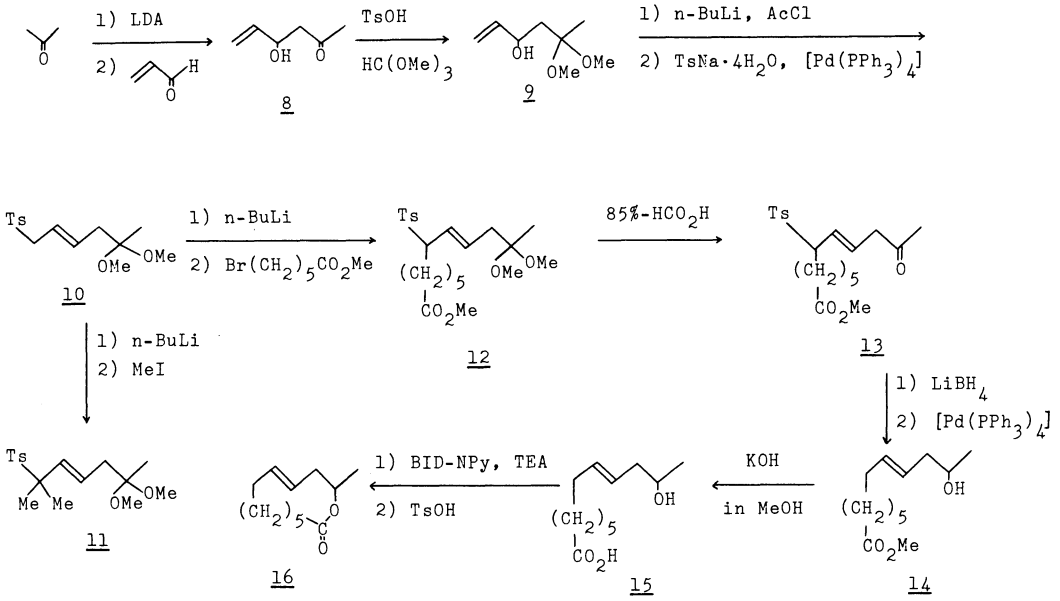
The starting materials (**5a**, **5c**, and **5d**) have been effectively made by modified Baeyer-Villiger oxidation[4] of the corresponding ketones. It was found that the addition of boron trifluoride etherate was quite effective for the oxidation of the ketones with *m*-chloroperbenzoic acid (MCPBA) in chloroform. The resulting lactones were directly saponified to give the corresponding ω-hydroxy carboxylic acids **5a**, **5c**, and **5d**, in 69, 78, and 82% yields, respectively.

Based on these results, we examined how to apply **1** to the synthesis of a naturally occurring macrolide, (±)-recifeiolide (**16**) isolated from *fungus Cephalosponim recifei*,[5] by the cyclization of (±)-11-hydroxy-(*E*)-8-dodecenoic acid (**15**).[6]

In the synthesis of **15**, one of the important points is the creation of the carbon–carbon double bond at C-8 of the chain with *E*-stereochemistry. In this regard, recently a convenient method for the preparation of allylic sulfones from the corresponding allylic acetate has been invented in our laboratory.[7] The stereochemistry of the double bond in the resulting allylic sulfones was completely *E*-form. Based on this finding, the synthesis of **16** was carried out according to



Scheme 2.



Scheme 3.

Scheme 3.

The reaction of acrylaldehyde with lithiated acetone in THF at −78°C gave the hydroxy ketone (**8**) in 89% yield. Acetalization of the carbonyl group of **8** by the use of 3 equiv of methyl orthoformate gave the compound (**9**) in 82% yield. The hydroxyl group of **9** was acetylated with *n*-BuLi and acetyl chloride. The crude acetate was converted to the corresponding sulfone (**10**) using a catalytic amount of $[Pd(PPh_3)_4]$ (5 mol%) and sodium *p*-toluenesulfinate in THF–MeOH in 78% yield from **9**. Stereochemistry[7,8] of the double bond in **10** was confirmed to be *E*-form by NMR spectrum of its dimethyl product (**11**), that is, the coupling constant between the two olefinic protons was 15.2 Hz. Treatment of the compound (**10**) with *n*-BuLi in the presence of HMPA, followed by the addition of 1.1 equiv of methyl 6-bromohexanoate, gave the alkylated product (**12**) in 90% yield. Deprotection of the acetal group of **12** by the treatment with 85% formic acid for 1 min at room temperature gave the keto ester (**13**) in 95% yield. Reduction of the carbonyl group to the alcohol and the subsequent detosylation[9] were accomplished in one-pot as follows: A solution of **13** in THF was treated with $LiBH_4$ at −10°C for 5 min and then $[Pd(PPh_3)_4]$ (6 mol%) was added. The mixture was allowed to stand for 1.5 h at room temperature to yield the hydroxy ester (**14**) in 72% yield. Its NMR and IR spectra were completely in accordance with the reported ones.[6] Hydrolysis of **14** with 40%-methanolic KOH solution gave the hydroxy acid (**15**) as a precursor of recifeiolide in 97% yield. It was lactonized using BID-NPy by high dilution method. The active ester derived from the reaction of **15** with **1** in 1,2-dichloroethane at −5°C was added slowly to a refluxing 1,2-dichloroethane containing 2 equiv of TsOH in a period of 15 h under N_2. The desired product (**16**) was separated in 81% yield with a preparative TLC.

As mentioned above, BID-NPy was found to be a versatile condensing reagent for the preparation of esters, peptides, and macrolides.

Experimental

All the melting points were determined with a micro melting apparatus (Yanagimoto-Seisakusho) and were uncorrected. The ^{1}H-NMR and IR spectra were recorded on JEOL JNM-PMX-60 and JASCO IRA-1 diffraction grating infrared spectrometer, respectively. The chemical shifts are recorded in the δ scale relative to TMS as an internal standard. For the reactions requiring slow addition, a Natume syringe pump, model KN-202, was used.

Materials. All the solvents were distilled and stored over a drying agent. Thin-layer chromatography (TLC) was performed on Merck's silica gel 60 PF_{254} (Art. 7749).

Preparation of BID-Cl. A mixture of $SOCl_2$ (10.62 g, 90 mmol) and saccharin (5.50 g, 30 mmol) was refluxed for 15 h in dioxane (100 ml) in the presence of active charcoal (0.8 g) and a catalytic amount of DMF (0.19 g, 2.6 mmol). The hot reaction mixture was filtered through celite to remove the charcoal. After evaporation of the solvent *in vacuo*, the resulting product was recrystallized from dry benzene. Yield, 4.60 g, 76%. Mp 145—147°C (lit, 143—145°C).[10] This BID-Cl was found to be unstable to moisture and thus was kept under vaccum.

Preparation of BID-NPy (1). To a suspension of BID-Cl (2.02 g, 10 mmol) and 5-nitro-2-pyridone (1.12 g, 8 mmol) in dry CH_3CN (25 ml) was added TEA (0.81 g, 8 mmol) at 0°C. A yellowish white crystalline precipitate started to separate almost immediately. After the suspension was stirred for 2 h at room temperature, the precipitate was filtered, washed with chloroform to remove triethylammonium chloride and recrystallized from CH_3CN to give pure BID-NPy (**1**) in 77% yield. 1.89 g, mp 239—241°C; IR (KBr) 3100, 1670, 1605, 1560, 1350, 1180 cm^{-1}; Found: C, 47.24; H, 2.18; N, 13.54%. Calcd for $C_{12}H_7N_3O_5S$: C, 47.22; H, 2.31; N, 13.77%.

Preparation of Esters from Carboxylic Acids and Alcohols. To a mixed suspension of **1** (152 mg, 0.5 mmol), phenylacetic acid (68 mg, 0.5 mmol), and benzyl alcohol (54 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) was added a solution of TEA (51 mg, 0.5 mmol) in CH_2Cl_2 (2 ml) at −10°C under N_2. The suspension became clear after a few minutes as the slightly soluble **1** was consumed in the progress of the reaction. The reaction mixture was gradually raised to room temperature.

After stirring overnight, the solvent was evaporated *in vacuo* and the resulting residue was taken up in AcOEt (30 ml). This was then washed successively with a saturated solution of $NaHCO_3$, with 1 mol dm^{-3} HCl, and with brine. The resulting residue was then subjected to preparative TLC (solvent; benzene: AcOEt=5:1, v/v) to afford 112 mg of benzyl phenylacetate, (95% yield). An oil.[17] IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ=3.50 (s, 2H), 4.98 (s, 2H), 7.13 (s, 5H), 7.15 (s, 5H).

The other esters shown in Table 1 were prepared in a similar manner.

Benzyl Cinnamate: IR (neat) 1710, 1630, 1160 cm^{-1}; NMR ($CDCl_3$) δ=5.09 (s, 2H), 6.29 (d, J=17 Hz, 1H), 7.22 (m, 10H). p-*Nitrophenyl Phenylacetate*: Mp 61—63 °C (lit, 62—63 °C).[18] 2,2,2-*Trichloroethyl Benzoate*: IR (neat) 1735, 1235, 1138 cm^{-1}; NMR ($CDCl_3$) δ=4.92 (s, 2H), 7.42—7.62 (m, 3H), 8.0—8.13 (m, 2H).[19] *Pentachlorophenyl Benzoate*: Mp 159—161 °C (lit, 159—160 °C).[19] p-*Nitrophenyl Benzoate*: Mp 142—144 °C (lit, 142 °C).[19] N-*(Benzoyloxy) Succinimide*: Mp 137—139 °C (lit, 139—140 °C).[17]

Preparation of Benzyloxycarbonyl Dipeptide Esters. Z-Cys(Bzl)-Gly-OEt: To a mixed suspension of **1** (152 mg, 0.5 mmol) and Z-Cys(Bzl)-OH (173 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) was added a solution of TEA (51 mg, 0.5 mmol) in CH_2Cl_2 (2 ml) dropwise at −10 °C under N_2. After stirring for 2 h at −10 °C, H-Gly-OEt·HCl (70 mg, 0.5 mmol) and a solution of TEA (51 mg, 0.5 mmol) in CH_2Cl_2 (2 ml) were successively added to the reaction mixture. The solution was stirred at 0 °C for 2 h and stirring was continued overnight at room temperature. The solvent was evaporated *in vacuo* and the resulting residue was taken up in AcOEt (30 ml). This was then successively washed with a saturated solution of $NaHCO_3$, with 1 mol dm^{-3} HCl, and with brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The resulting residue was subjected to preparative TLC (solvent; benzene: AcOEt=1:1, v/v) to separate the desired product. Recrystallization from benzene-hexane gave the product, Z-Cys(Bzl)-Gly-OEt, in quantitative yield (208 mg).

In a similar manner, various benzyloxycarbonyl dipeptide esters were prepared, as shown in Table 2.

*Lactonization of ω-Hydroxy Carboxylic Acids. 12-Dodecanolide (**6b**)*: To a suspension of **5b** (43 mg, 0.2 mmol) and **1** (61 mg, 0.2 mmol) in 1,2-dichloroethane (95 ml) was added a solution of TEA (21 mg, 0.2 mmol) in 1,2-dichloroethane (5 ml) dropwise at −0 °C in a period of 10 min under N_2. After about 30 min the initial suspension became a clear yellowish solution. Stirring was continued for about 1 h to complete the formation of the active ester. The resulting reaction mixture containing the active ester was added slowly to a refluxing dry 1,2-dichloroethane (50 ml) containing anhydrous TsOH (76 mg, 0.4 mmol) with a mechanically driven syringe in a period of 6 h. After the addition, it was further refluxed for 2 h. The solvent was evaporated *in vacuo* and the resulting residue was partitioned between water and AcOEt. The AcOEt layer was successively washed with 10% $NaHCO_3$, 1 mol dm^{-3} HCl, and brine. The solution was dried over Na_2SO_4 and was evaporated *in vacuo*. The resulting residue was subjected to preparative TLC (solvent; hexane:ether=10:1, v/v). Two fractions were obtained. From the first fraction (R_f=0.64), monolide was obtained as an oil (28 mg, 71%). Its spectral data (IR, NMR), behavior on TLC, and GLC were identical with the authentic sample. MS m/z 198 (M^+); IR (neat) 1735, 1245 cm^{-1}; NMR ($CDCl_3$) δ=1.1—2.0 (m, 18H), 2.35 (t, J=6 Hz, 2H), 4.15 (t, J=6 Hz, 2H). The crystalline substance obtained from the second fraction (R_f=0.52) was found to be the dimeric lactone by comparison with the authentic sample. 7 mg, 18%; mp 102—103 °C (lit, 103—104 °C).[3b]

Other ω-hydroxy carboxylic acids (**5a**, **5c—g**) were cyclized in a similar manner.

6a: An oil, MS m/z 184 (M^+); IR (neat) 2930, 2870, 1738, 1465, 1440, 1350, 1245, 1170, 1140, 1090 cm^{-1}; NMR ($CDCl_3$) δ=1.15—1.84 (m, 16H), 2.31 (t, J=6 Hz, 2H), 4.01 (t, J=6 Hz, 2H).

6c: An oil, MS m/z 212 (M^+); IR (neat) 2930, 2845, 1730, 1460, 1370, 1285, 1258, 1225, 1170, 1100 cm^{-1}; NMR ($CDCl_3$) δ=1.06—1.83 (m, 20H), 2.30 (t, J=6 Hz, 2H), 4.13 (t, J=6 Hz, 2H).

6d: Mp 35—36 °C (lit, 34 °C).

6e: After the addtion of the active ester, the reaction mixture was further refluxed for 10 h. MS m/z 254 (M^+); IR (neat) 2940, 2845, 1730, 1460, 1380, 1350, 1250, 1160 cm^{-1}; NMR ($CDCl_3$) δ=1.16—1.83 (m, 26H), 2.30 (t, J=6 Hz, 2H), 4.15 (t, J=6 Hz, 2H).

6f: An oil, MS m/z 282(M^+); IR (neat) 2920, 2860, 1725, 1470, 1370, 1320, 1245, 1170, 1138 cm^{-1}; NMR ($CDCl_3$) δ=0.93 (t, J=7 Hz, 3H), 1.03—1.86 (m, 28), 2.35 (t, J=6 Hz, 2H), 4.70—5.00 (m, 1H).

6g: An oil, MS m/z 280 (M^+); IR (neat) 2920, 2850, 1720, 1640, 1440, 1360, 1230, 1170 cm^{-1}; NMR ($CDCl_3$) δ=0.93—1.01 (t, J=7 Hz, 3H), 1.02—1.93 (bm, 24H), 2.10—2.46 (bt, 2H), 3.50—4.01 (bm, 1H), 5.35—5.56 (m, 2H).

*Preparation of ω-Hydroxy Carboxylic Acids (**5a**, **5c**, and **5d**). 13-Hydroxytridecanoic Acid (**5c**)*: A solution of cyclotridecanone (0.98 g, 5 mmol) in CH_2Cl_2 (30 ml) was treated with freshly distilled boron trifluoride etherate (0.85 g, 6 mmol) for 15 min. To the reaction mixture was added MCPBA (purity 70%, 2.59 g, 15 mmol) in a period of about 20 min and the reaction mixture was stirred for 15 h at 40 °C. The mixture was cooled and water was added to it. The excess peroxy acid was destroyed by the dropwise addition of 10% solution of Na_2SO_3 and then the layers were separated. The aqueous portion was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The crude lactone thus obtained was directly subjected to alkaline hydrolysis with 1 mol dm^{-3} NaOH in methanol and water (4:1). The solution was heated at 60 °C for 1 h. After cooling, the mixture was concentrated to half the volume, diluted with water, and washed with chloroform. The aqueous layer was acidified with 1 mol dm^{-3} HCl (pH=3) at 0 °C to give a crystalline substance. After standing for about 1 h, the precipitate was filtered and recrystallized from 1,2-dichloroethane to give **15c** (0.90 g, 78%). Mp 78—79 °C (lit, 79 °C).[20]

In a similar manner, other carboxylic acids were prepared from the corresponding cycloalkanones.

*11-Hydroxyundecanoic Acid (**5a**)*: 69%, mp 65—67 °C (lit, 66 °C).[21]

*15-Hydroxypentadecanoic Acid (**5d**)*: 82%, mp 80 °C (lit, 82—84 °C).[19]

Preparation of Methyl 6-Bromohexanoate: 6-Bromohexanoic acid prepared by the reported method[19] was treated with diazomethane in ether. Distillation of the crude product gave pure oily product: Bp 72—78 °C/1 Torr: IR (neat) 2950, 1730, 1432, 1251, 1200, 1168 cm^{-1}; NMR ($CDCl_3$) δ=1.30—2.13 (m, 6H), 2.30 (t, J=6 Hz, 2H), 3.37 (t, J=6 Hz, 2H), 3.63 (s, 3H).

*4-Hydroxy-5-hexen-2-one (**8**).* To a solution of diisopropylamine (1.11 g, 11 mmol) in THF (15 ml) was slowly added a solution of *n*-BuLi (*ca.* 15% in hexane, 6.68 ml, 10 mmol) dropwise at −50 °C under N_2. After stirring for about 1 h at −50 °C to −30 °C, the reaction mixture was cooled to −78 °C and a solution of acetone (5.80 g, 10 mmol) in THF (5 ml) was slowly added to the reaction mixture during 1 h. The reaction mixture was stirred for about 30 min at −78 °C to −30 °C and again the temperature was cooled to −78 °C. A solution of acrylaldehyde

(6.72 g, 12 mmol) in THF (2 ml) was added all at once. After 5 min, the reaction mixture was quenched with CH_3OH-HCl. The solution was evaporated to dryness and the residue was partitioned between ether and water. The resulting mixture of products was separated by column chromatography (silica gel, solvent; benzene: AcOEt=3:1 v/v). The desired product was obtained in 89% yield (1.02 g). IR (neat) 3400, 2980, 2930, 1700, 1640, 1420, 1365, 1160, 1120, 1060, 990, 925 cm^{-1}; NMR ($CDCl_3$) δ=2.20 (s, 3H), 2.63 (d, J=6 Hz, 2H), 3.50 (s, 1H), 4.33—4.70 (bm, 1H), 4.94—6.21 (bm, 3H).

5,5-Dimethoxy-1-hexen-3-ol (9). To a solution of **8** (342 mg, 3 mmol) in MeOH (15 ml) in the presence of Molecular Sieves (4A, 1/16, 3 g) was added trimethyl orthoformate (1.32 ml, 12 mmol) at room temperature under N_2. A catalytic amount of TsOH (68 mg, 12 mol%) was added to the reaction mixture and, after stirring for 3 h, it was made slightly basic (pH=8) by adding a saturated solution of Na_2CO_3. The MeOH was removed *in vacuo* and the resulting residue was taken up in chloroform (40 ml). The organic layer was washed with water three times, dried over Na_2SO_4, and evaporated. The resulting residue was subjected to preparative TLC (solvent; benzene: AcOEt=2:1, v/v) to give 393 mg of the desired product (82%). IR (neat) 3460, 3080, 2960, 2840, 1640, 1450, 1420, 1370, 1265, 1220, 1140, 1040, 985, 920 cm^{-1}; NMR ($CDCl_3$) δ=1.26 (s, 3H), 1.80 (bm, 2H), 3.01 (s, 6H), 3.63 (s,1H), 4.13—4.53 (bm, 1H), 4.90—6.20 (bm, 3H).

5,5-Dimethoxy-1-tosyl-2-hexene (10). n-BuLi (3 mmol) was added dropwise to a solution of **9** (480 mg, 3 mmol) in THF (6 ml) at −78 °C under N_2. The mixture was stirred for about 30 min. To the reaction mixture was added a solution of acetyl chloride (273 mg, 3.5 mmol) at −78 °C. After 10 min, the reaction was found to be complete and the mixture was quenched with a buffer solution of K_2HPO_4-NaOH (pH=7). The solvent was evaporated and the residue was taken up in chloroform. The chloroform solution was washed with a small amount of water, dried, and evaporated. The crude product was obtained in quantitative yield and used in the subsequent reaction. IR (neat) 2940, 2840, 1738, 1640, 1420, 1370, 1240, 1040, 925, 845, 800 cm^{-1}; NMR ($CDCl_3$) δ=1.33 (s, 3H), 2.08 (s, 3H) 1.95—2.35 (bm, 2H), 3.20 (s, 6H), 4.95—6.10 (bm, 5H).

Sodium p-Toluenesulfinate Tetrahydrate (0.8 g, 3.2 mmol) was dissolved in MeOH (2 ml) and THF (4 ml) at room temperature under N_2. The crude acetylated compound obtained above (*ca.* 3 mmol) in THF (2 ml) was added to it. A solution of [$Pd(PPh_3)_4$] (174 mg, 0.15 mmol) in THF (2 ml) was added to the reaction mixture. After 30 min, the clear brownish solution changed to light yellow, accompanied by precipitation, and gradually it turned lemon yellow. After stirring overnight, KCN (36 mg) dissolved in a minimum amount of water was added to the reaction mixture. The solution became colorless. The solvent was evaporated *in vacuo* and the resulting residue was dissolved in CH_2Cl_2 (40 ml) and the insoluble materials were filtered. The filtrate was dried over Na_2SO_4. After removal of the solvent, the residual oil was subjected to preparative TLC (solvent; hexane: AcOEt=2:1, v/v) to give the desired product (**10**) (698 mg, 78%) from **9**. MS m/z 267 (M^+—OMe); IR (neat) 2960, 1735, 1595, 1380, 1360, 1310, 1295, 1280, 1230, 1138, 1080, 1030, 960, 805, 725 cm^{-1}; NMR ($CDCl_3$) δ=1.06 (s, 3H), 2.20—2.40 (bm, 2H), 2.46 (s, 3H), 3.10 (s, 6H), 3.76 (d, J=6 Hz, 2H), 5.30—5.67 (bm, 2H), 7.20 (d, J=8 Hz, 2H), 7.60 (d, J=8 Hz, 2H).

6,6-Dimethoxy-2-methyl-2-tosyl-3-heptene (11). To a solution of **10** (100 mg, 0.34 mmol) in THF (4 ml) was added one equiv of n-BuLi (0.34 mmol) dropwise at −78 °C under N_2. After 10 min, hexamethylphosphoric triamide (HMPA) (0.4 ml) was added and then after 1 h, a solution of CH_3I (53 mg, 0.37 mmol) in THF (1.5 ml) was dropwise added. The reaction mixture was stirred for 2 h at −78 °C, warmed to room temperature, and then cooled down at −78 °C again. This alkylation procedure was repeated once again. The crude material was purified by preparative TLC (solvent; hexane:AcOEt=2:1, v/v) to afford **11** in 53% yield. MS m/z 295(M^+—OMe); IR (neat) 2940, 1590, 1292, 1170, 1150, 1120, 972, 810 cm^{-1}; NMR ($CDCl_3$) δ=1.13 (s, 3H), 1.43 (s, 6H), 2.35 (d, J=7 Hz, 2H), 2.42 (s, 3H), 3.14 (s, 6H), 5.27 (dd, J=7, 15.2Hz, 1H), 5.60 (d, J=15.2 Hz, 1H), 7.23 (d, J=8 Hz, 2H), 7.57 (d, J=8 Hz, 2H).

Methyl (E)-11,11-Dimethoxy-7-tosyl-8-dodecenoate (12). To a solution of **10** (570 mg, 1.91 mmol) in THF (10 ml) was added 1.1 equiv of n-BuLi at −78 °C under N_2, followed by the addition of HMPA (2 ml) after 20 min. After 1 h, a solution of methyl 6-bromohexanoate (439 mg, 2.10 mmol) in THF (5 ml) was dropwise added in a period of 20 min at −78 °C. The reaction mixture was allowed to stand overnight at room temperature. The usual work-up gave an oily crude product which was purified by preparative TLC (solvent; hexane:AcOEt=2:1, v/v). Yield was 90% (an oil, 737 mg). MS m/z 395 (M^+—OMe); IR (neat) 2950, 1729, 1590, 1295, 1140, 1080, 1045, 968, 805, 750 cm^{-1}; NMR ($CDCl_3$) δ=1.10 (s, 3H), 1.13—2.50 (m, 12H), 2.40 (s, 3H), 3.10 (s, 6H), 3.20—3.53 (m, 1H), 3.60 (s, 3H), 5.17—5.47 (m, 2H), 7.27 (d, J=8 Hz, 2H), 7.56 (d, J=8 Hz, 2H).

Methyl (E)-11-Hydroxy-8-dodecenoate (14). The compound(**12**) (616 mg, 1.45 mmol) was dissolved in 85% formic acid (4.5 ml). The formic acid was immediately removed *in vacuo* to give a residue which was taken up in AcOEt. The organic solution was washed with 10% $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent gave an oily keto ester (**13**) in 95% yield, which was used in the subsequent reaction without further purification. IR (neat) 2930, 1722, 1710, 1595, 1295, 1135, 1080, 965, 810 cm^{-1}; NMR ($CDCl_3$) δ=1.03—2.37 (m, 12H), 2.03 (s, 3H), 2.43 (s, 3H), 3.08 (d, J=6 Hz, 2H), 3.23—3.57 (m, 1H), 3.63 (s, 3H), 5.27—5.60 (m, 2H), 7.34 (d, J=8 Hz, 2H), 7.59 (d, J=8 Hz, 2H).

To a solution of **13** (86 mg, 0.23 mmol) in THF (2 ml) was added $LiBH_4$ (910 mg, 0.5 mmol) in one portion at −10 °C under N_2. After 5 min, 6 mol% of [$Pd(PPh_3)_4$] (16 mg) dissolved in THF (2 ml) was added to the reaction mixture at −10 °C. The reaction mixture was stirred for 1.5 h at room temperature. The color of the solution gradually changed into dark brown. The reaction mixture was quenched with water. The THF was removed *in vacuo* to give a residue which was taken up in AcOEt. The AcOEt solution was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was subjected to preparative TLC (solvent; hexane:AcOEt=4:1, v/v) to give the desired product (**14**) in 72% yield (37 mg) from **13**. Its IR and NMR data were in accord with the reported ones.[6b] CI-MS m/z 229 (M^++1); IR (neat) 1730, 962 cm^{-1}; NMR ($CDCl_3$) δ=1.07—1.77 (d, J=6 Hz, 3H), 1.17 (d, J=6 Hz, 3H), 1.77—2.47 (m, 6H), 3.43—4.02 (m, 1H), 3.60 (s, 3H), 5.13—5.47 (m, 2H).

(±)-(E)-11-Hydroxy-8-dodecanoic Acid (15). To **14** (424 mg, 1.86 mmol) was added 6 mol dm^{-3} methanolic KOH solution (3.8 ml) at room temperature. Water (2 ml) was added to the solution and the reaction mixture was stirred for 1 h at room temperature and extracted with ether three times. The aqueous layer was acidified with 6 mol dm^{-3} HCl. The separated oil was extracted with chloroform. The organic solution was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded **15** in 97% yield (386 mg). IR and NMR data of **15** thus obtained were in good agreement with the reported ones.[6a] IR (neat) 1700, 965 cm^{-1}; NMR ($CDCl_3$) δ=1.00—1.80 (m, 8H), 1.17 (d, J=6 Hz, 3H), 1.80—

2.53 (m, 6H), 3.50—4.10 (m, 1H), 5.20—5.43 (m, 2H), 6.93 (bs, 2H).

(±)-(E)-8-Dodecen-11-olide, Recifeiolide (16). To a suspension of **15** (50 mg, 0.23 mmol) and **1** (78 mg, 0.25 mmol) in 1,2-dichloroethane (180 ml) was added a solution of TEA (24 mg, 0.23 mmol) in 1,2-dichloroethane (5 ml) dropwise at −5 °C. After about half an hour, the initial suspension became a clear yellowish solution. It was diluted with 1,2-dichloroethane (60 ml). The reaction mixture was added slowly to a refluxing 1,2-dichloroethane containing anhydrous TsOH (88 mg, 0.46 mmol) with a mechanically driven syringe under N_2. After completion of the addition, it was further refluxed for 2 h. The solvent was evaporated and the resulting residue was partitioned between AcOEt and water. The AcOEt portion was washed successively with 10% $NaHCO_3$ and brine. After drying, the resulting residue was subjected to preparative TLC (solvent; hexane: AcOEt=8:1, v/v) to give the desired product (**16**) (37 mg, 81%). Its spectral data were completely in accordance with the reported values.[6] An oil; CI-MS *m/z* 197(M^++1); IR (neat) 1720, 1245, 965 cm^{-1}; NMR ($CDCl_3$) δ=1.23 (d, J=6 Hz, 3H), 1.10—1.90 (m, 8H), 1.90—2.77 (m, 6H), 4.60—5.00 (m, 1H), 5.00—5.50 (m, 2H).

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