JOC The Journal of Organic Chemistry

Article

Asymmetric Total Synthesis of Putative Structure of Diplopyrone

Saurabh Maity, Suresh Kanikarapu, Kanakaraju Marumudi, Ajit C. Kunwar, Jhillu S. Yadav, and Debendra Kumar Mohapatra

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00086 • Publication Date (Web): 07 Apr 2017

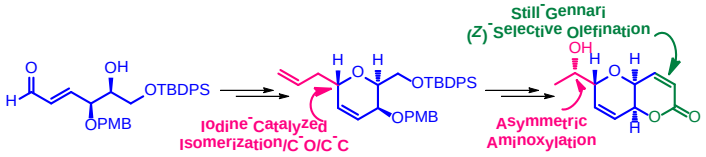
ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Asymmetric Total Synthesis of Putative Structure of Diplopyrone

Saurabh Maity,[†,‡] Suresh Kanikarapu,[†] Kanakaraju Marumudi,[Ī] Ajit C. Kunwar,[Ī] Jhillu S. Yadav,[†,‡] and Debendra K. Mohapatra*[†,‡]

[†]Natural Products Chemistry Division, [Ī]Centre for NMR and Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India; [‡]Academy of Scientific and Innovative Research (AcSIR, Mathura Road, New Delhi-110 025, India; mohapatra@iict.res.in



ABSTRACT: The first asymmetric total synthesis of the putative structure of diplopyrone was achieved in 17 linear steps starting from *cis*-1,4-butene-diol. The synthetic route features iodine-catalyzed tandem isomerization followed by C-O and C-C bond formation reaction strategy developed by our own group to construct the *trans*-2,6-disubstituteddihydropyran ring, asymmetric *α*-aminoxylation reaction, and Still-Gennari (*Z*)-selective olefination reactions. Careful comparison of ^{1}H and ^{13}C NMR spectroscopic data as well as investigation of the UV and circular dichroism (CD) spectrum in trifluoroethanol for compound **2**, suggest that the the putative structure proposed for diplopyrone {6-[(1*S*)-1-hydroxyethyl]-2,4a(*S*),6(*R*),8a(*S*)-tetrahydropyran[3,2-*b*]pyran-2-one} requires revision.

INTRODUCTION

5,6-Dihydropyran-2-one moiety containing natural products were isolated from many sources such as bacteria, microbial plants and insects and is a key biosynthetic intermediate often involved in many different types of biological processes [1] These compounds show interesting biological activities such as neurotoxic, antibiotic, antifungal, immunosuppressive, anti-inflammatory, cytotoxic, antitumor activities.[2] It was postulated that some of these pharmacological effects may be related to the presence of the conjugated double bond which acts as a Michael acceptor.[3] The important structural motif, pyranopyran occurs in active substance like botcinin D (**1**; *trans*-fused),[4] diplopyrone (**2**; *cis*-fused),[5] and thyrsiferol (**3**; *trans*-fused)[6] which were shown in Figure 1.

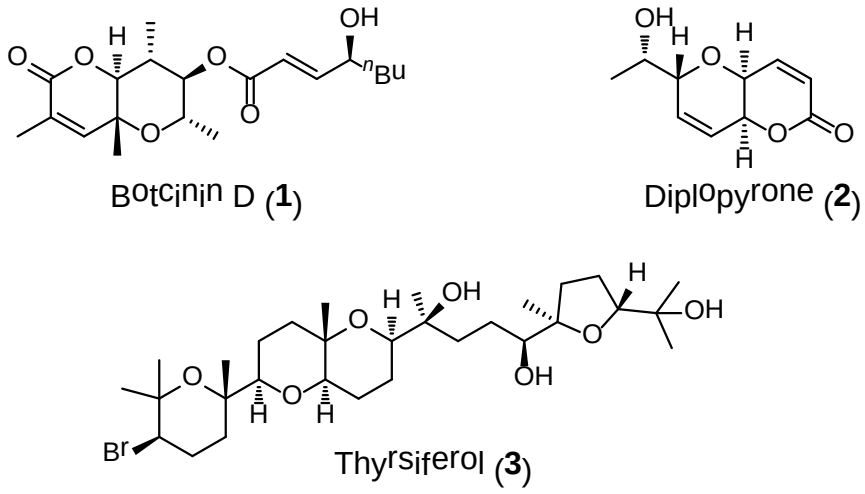


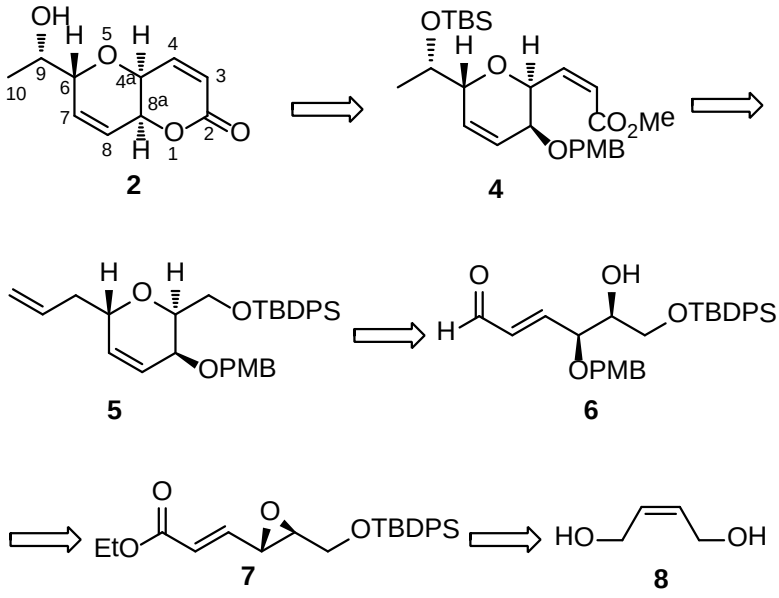
Figure 1. Naturally occurring pyranopyrans moiety containing natural products.

Diplopyrone (**2**), is a new phytotoxic monosubstituted tetrahydropyranpyran-2-one, isolated from liquid culture filtrates of "*Diplodia mutila*".[5] This pathogenic fungus is responsible for coak oak decline due to formation of canker disease. The fungus also can engross plants of different

age, inducing signs very similar to those produced by tracheomycotic disease. Considering the massive commercial use of cork, this causes heavy fiscal losses and environmental damages. On tomato, a nonhost plant, diplopyrone also causes brown discoloration or simmering on the stem. Diplopyrone (**2**) also acts as an antimicrobial agent. From the structural perspective, diplopyrone contains a *cis*-fused bicyclic structure in which six-membered cyclic ether is fused with a six-membered lactone. The stereochemistry of diplopyrone was proposed based on spectroscopic and chemical methods as 6-[(1*S*)-1-hydroxyethyl]-2,4a(*S*),6(*R*),8a(*S*)-tetrahydropyran[3,2-*b*]pyran-2-one (**2**) and the absolute stereochemistry of the chiral secondary hydroxy center in the exocyclic tail was determined following modified Mosher's ester method.[2] As part of our ongoing program on total synthesis of pyran containing natural products,[7] herein, we report a liner first total synthesis of diplopyrone (**2**) and assign the absolute stereochemistry.

Retrosynthetic analysis for the synthesis of diplopyrone (**2**) is shown in Scheme 1. Diplopyrone (**2**) could be obtained from ester **4** following deprotection and *in situ* lactonization. *cis*-Ester moiety present in **4** would result from Still-Ginneri reaction and non-allylic secondary hydroxyl group could be installed *via* asymmetric *α*-aminoxylation reaction starting from compound **5**. *trans*-Dihydropyran **5** could be prepared from *δ*-hydroxy-*α*,*β*-unsaturated aldehyde **6** by using our own strategy involving iodine-catalyzed tandem isomerization of enal, followed by C-O and C-C bond formation reaction . Aldehyde **6** can be prepared through regioselective opening of *γ*,*δ*-epoxy-*α*,*β*-unsaturated ester **7** which could be synthesized from easily available and inexpensive *cis*-butene-1,4-diol (**8**).

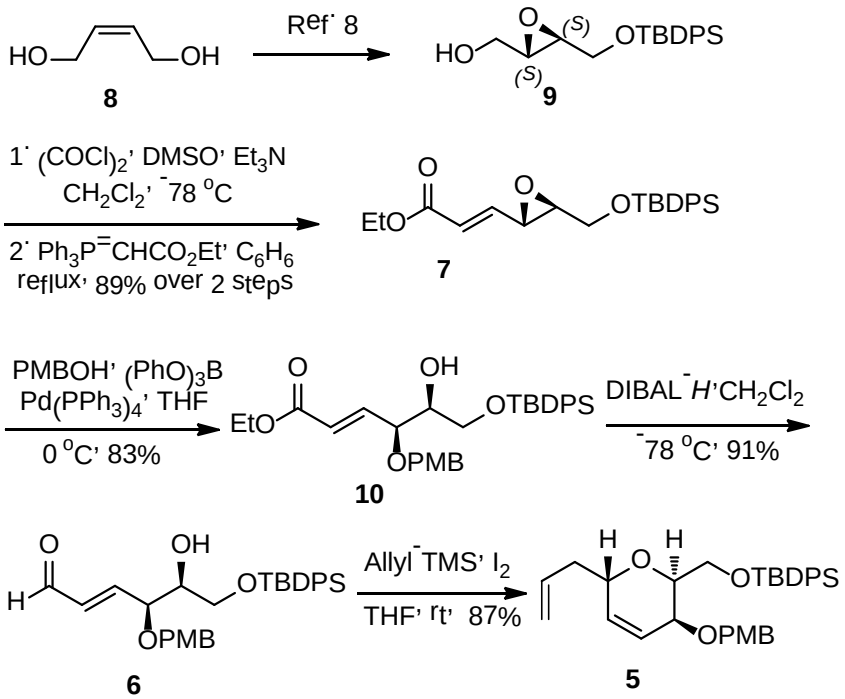
Scheme 1. Retrosynthetic Analysis



RESULTS AND DISCUSSION

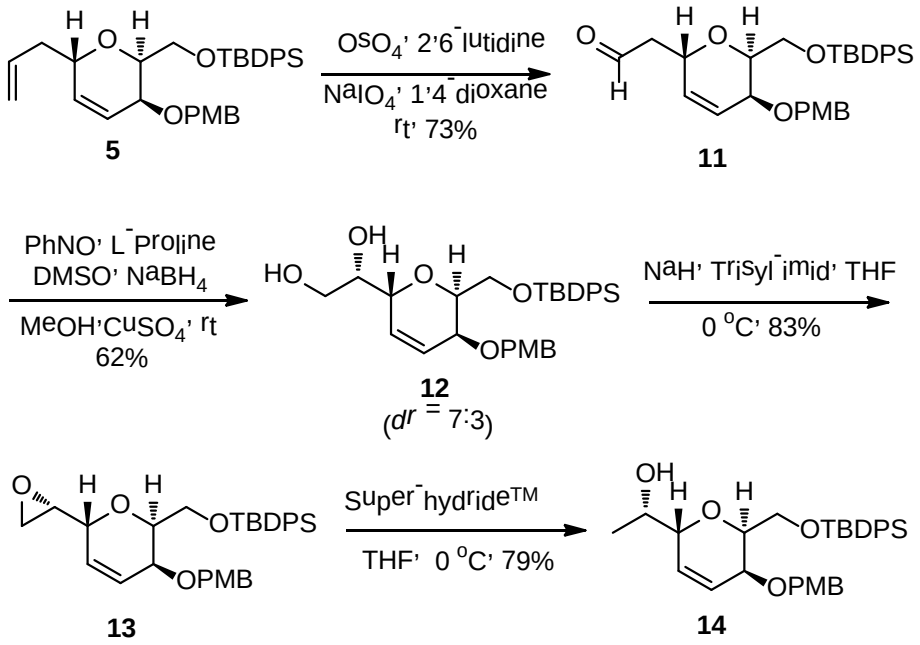
The synthesis was initiated with the synthesis of **9** from commercially available *cis*-butene-1,4-diol **8** following a known literature protocol.[8] Oxidation of the primary alcohol **9** under Swern oxidation conditions[9] followed by two carbon homologation using Witting olefination reaction[10] afforded the unsaturated epoxy ester **7** in 89% yield for two steps. Regioselective opening of the epoxide in **7** with *p*-methoxybenzyl alcohol (PMB-OH) in presence of $(PhO)_3B$ and catalytic amount of Pd(0)-catalyst gave the unsaturated ester **10** in 83% yield.[11] Ester in **10** was reduced to the aldehyde **6** using DIBAL-*H* at −78 °C in good yield. Using a protocol developed in our group for the synthesis of dihydropyrans, treatment of the aldehyde **6** with allyl-TMS in presence of catalytic amount of molecular iodine afforded the *trans*-dihydropyran **5** in 96:4 diastereomeric ratio in 87% yield (HPLC method) (Scheme 2).[12]

Scheme 2. Synthesis of the Allylated Pyran Fragment 5



Selective oxidative cleavage of the terminal double bond following Jin's protocol[13] with OsO_4, 2,6-lutidine, $NaIO_4$ furnished the aldehyde **11** in 73% yield. α-Aminohydroxylation of the aldehyde **11** with L-proline and nitrosobenzene in dry DMSO, followed by *in situ* reduction of the aldehyde with $NaBH_4$ and the cleavage of resulting '*O-N*' bond by $CuSO_4$ produced the diol **12** in 62% yield over 2 steps with moderate diastereoselectivity (dr =7:3, determined by HPLC).[14] The diastereomers were not separated at this stage by silica gel column chromatography and was used in the next step. Following the Forsyth protocol,[15] exposure of diol **12** with NaH and tosylimidazole furnished the epoxide **13** in 83% combined yield (7:3 ratio). At this stage, diastereomers were easily separated by silica gel column chromatography. The major diastereomer was taken forward. Treatment of epoxide **13** with super-hydride in anhydrous THF furnished alcohol **14** in good yield (Scheme 3).[16]

Scheme 3. Synthesis of the Key Fragment 14



Absolute stereochemistry of the newly generated secondary hydroxy bearing carbon center (C7) was determined by modified Mosher's ester analysis.[17] Esterification of the alcohol **14** with both *(S)*- and (*R*)-methoxy-*α*-(trifluoromethyl)phenylacetic acid (MTPA) showed positive chemical shift difference [($\Delta\delta = \delta_S - \delta_R$) × 10^3] for protons on C6 through C8, while protons on C10 showed negative chemical shift differences, which is the indicative of C9 bearing an *S*-configuration (Figure 2).

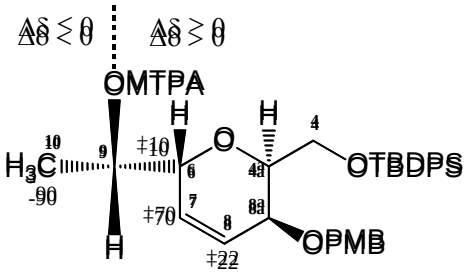
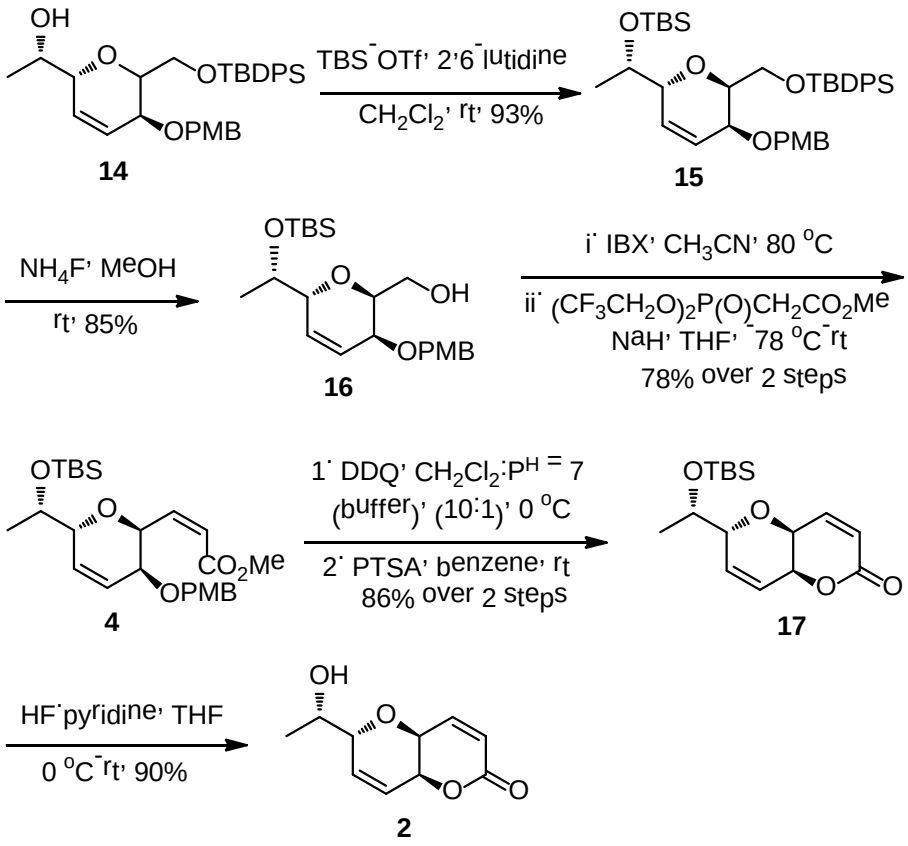


Figure 2. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for *R* and *S*-MTPA ester of alcohol **14**.

Having secured the stereochemistry of the newly generated center of the secondary hydroxy group present in **14**, the hydroxy group was protected as its TBS-ether **15** using *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine as base in CH_2Cl_2 in 93% yield. Primary silylether in **15** was selectively deprotected in presence of NH_4F in MeOH at room temperature to afford the primary alcohol **16** in 85% yield.[18] Treatment of alcohol **16** with 2-iodoxybenzoic acid (IBX) in acetonitrile at 80 °C, furnished the corresponding aldehyde in quantitative yield.[19] Following Still-Gennari conditions,[20] treatment of the crude aldehyde with *bis*-(trifluoroethyl)methyl phosphonate in the presence of NaH in THF at −78 °C provided (*Z*)-*α*,*β*-unsaturated ester **4** in 78% yield. PMB-group was deprotected with DDQ[21] in CH_2Cl_2/buffer (pH = 7) (9:1) to afford the, which was lactonized using a catalytic amount of PTSA in benzene to furnish the lactone **17** in 86% yield over two steps. Deprotection of the TBS group in lactone **17** under usual conditions (TBAF/THF or CSA/MeOH) led to intractable mixture of products. Pleasingly, treatment of lactone **17** with HF.pyridine[22] in dry THF led to clean deprotection of TBS-ether to furnish diplopyrone **2** in 90% yield (Scheme 4).

Scheme 4. Completion of the Total Synthesis of Diplopyrone (2)



However, comparison of the ^{1}H and ^{13}CNMR spectra (Table 1) of the synthetic sample with that of the natural product displayed discrepancies concerning the resonances of some of the protons and carbons.

Table 1: Comparison of ^{1}H and ^{13}C NMR of Natural Product with Synthetic 2 in $CDCl_3$ (500 MHz)

Position	^{1}H NMR Natural	^{1}H NMR Synthetic **2**	^{13}C NMR Natural	^{13}C NMR Synthetic **2**
2			162.7	161.73
3	6.23 (d, *J* = 9.8 Hz)	6.07 (dd, *J* = 10.0, 1.6 Hz)	124.8	123.28
4	6.88 (dd, *J* = 9.8, 5.8 Hz)	6.88 (ddd, *J* = 10.0, 3.1, 1.0 Hz)	140.0	144.24
4a	4.09 (dd, *J* = 5.8, 2.8 Hz)	4.92 (ddd, *J* = 5.6, 3.1, 1.6 Hz)	64.9	64.90
6	4.16 (br s)	4.08 (ddt, *J* = 4.2,	78.9	74.79

		2.6, 2.6, 1.6 Hz)		
7	6.18 (d, *J* = 9.8 Hz)	6.06 (td, *J* = 10.5, 1.6, 1.6 Hz)	132.6	129.57
8	6.14 (ddd, *J* = 10.4, 4.6, 1.8 Hz)	6.04 (td, *J* = 10.5, 2.6, 2.6 Hz)	123.0	124.68
8a	4.65 (ddd, *J* = 4.6, 3.5, 2.8 Hz)	4.97 (m, *J* = 5.6, 2.6, 2.6, 1.6, 1.0 Hz)	69.7	70.0
9	3.92 (dq, 6.5, 4.2 Hz)	3.96 (dd, *J* = 6.4, 4.2 Hz)	69.03	69.66
10	1.21 (d, *J* = 6.5 Hz)	1.25 (d, *J* = 6.4 Hz)	17.8	18.72

Extensive NMR studies on the synhtetic sample of (obtained above) diplopyrone (**2**) were carried out in $CDCl_3$ solvent with the help of 2-D Double Quantum Filtered Correlation Spectroscopy (DQFCOSY), Nuclear Overhauser Effect Spectroscopy (NOESY), Hetero-Nuclear Single Quantum Correlations (HSQC), Hetero-Nuclear Multiple Bond Correlation (HMBC) and extensive decoupling experiments. The olefinic protons of α,β-unsaturated δ-lactone (H-3 and H-4), displayed very distinctive pattern at 6.88 (ddd, 10.0, 3.1, 1.0 Hz) and 6.07 (dd, 10.0, 1.6 Hz) ppm in the ^{1}H NMR spectrum. In addition, these two protons displayed HMBC correlation with lactone carbonyl carbon (161.73 ppm). The other group of (Z)-olefinic protons H-7 and H-8 ($^3J_{H\text{-}7/H\text{-}8}$ = 10.5 Hz) resonated at 6.06 and 6.04 ppm, resulting in a somewhat complicated spectral pattern. Further assignments were completed with the help of DQF-COSY and NOESY experiments. The very distintive dq at 3.96 ppm assigned as H-9 due to adjacent correlations with coupled Me-10 (1.25 ppm) and proton H-6 (4.08 ppm) in the DQF-COSY spectrum. The DQF-COSY spectrum showed H-4 coupled to adjacent bridged proton H-4a, which resonated as ddd at 4.92 ppm ($^3J_{H\text{-}4/H\text{-}4a}$ = 3.1 Hz). Further H-4a coupled to another bridged proton H-8a, appeared as ddd at 4.97 ppm with coupling constant, $^3J_{H\text{-}4/H\text{-}8a}$ = 5.6 Hz, justifying a *syn*-orientation of bridged protons (H-4a and H-8a) (Table 1). The stereochemistry of bicyclic

compound was assigned with the help of couplings discussed above and NOE correlations, H-4/H-6, H-6/Me-10 and H-7/Me-10. The energy minimized structure adequately supported the proposed structure of diplopyrone (**2**) (Figure 3). The sign of the specific rotation of the synthetic compound was same {$[\alpha]_D^{25}$ = +49.0 (*c* = 0.28, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ +67.6 (*c* = 0.25, $CHCl_3$)}, but the value was showing little deviation from that reported for the natural product. However, comparison of the UV and CD spectra of the natural product (Figure 3) and the synthetic sample (Figure 4) in trifluoroethanol, showed reasonable agreement with the pattern as well as the values for the cotton effects studied by Evdente et al indicating that the functionalties present in the molecule are similar.[5b] Considering the above extenisive NMR studies, it is suggested that the putative structure proposed for diplopyrone requires revision.

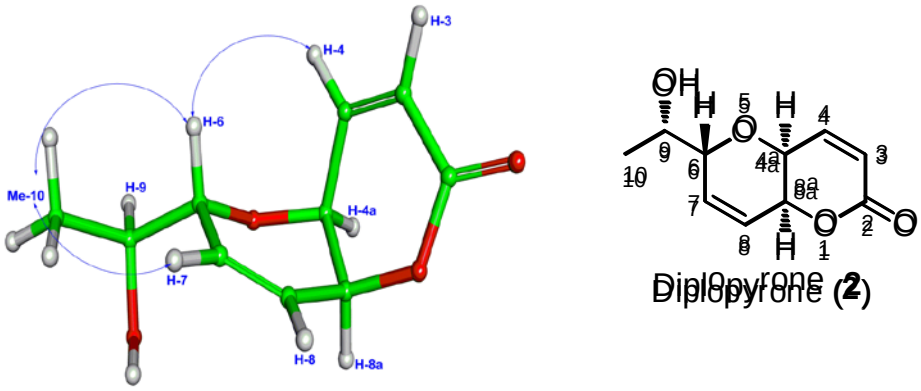


Figure 3: Energy minimized structure of diplopyrone (**2**) along with the characteristic NOE correlations shown with double-headed arrows.

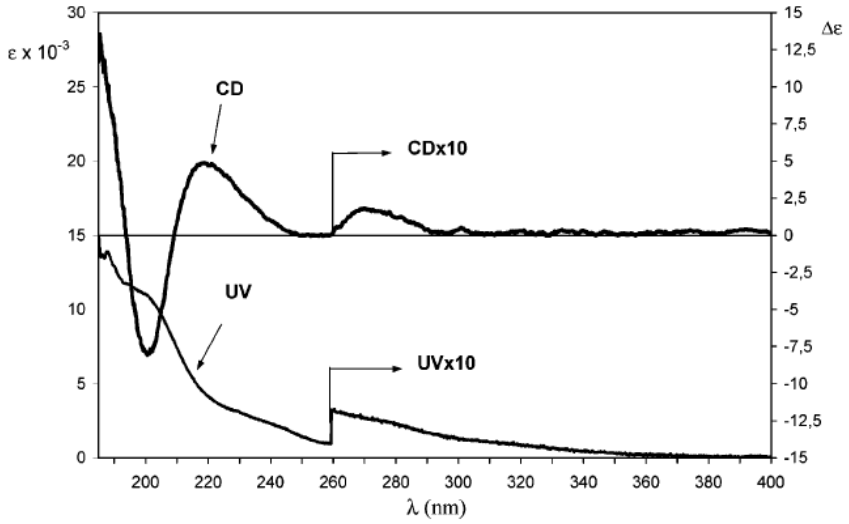


Figure 4. Absorption (UV) and circular dichroism (CD) spectra of natural diplopyrone in trifluoroethanol (taken from Evidente et al. *J. Org. Chem.* **2005**, *70*, 7-13)

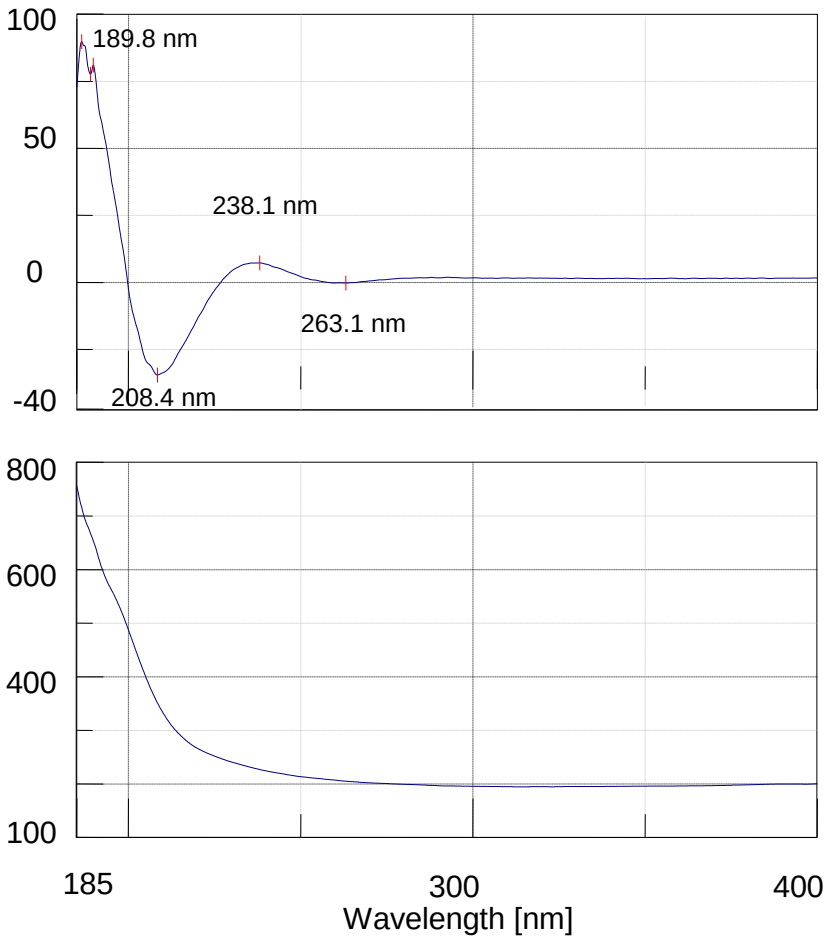


Figure 5. Absorption (UV) and circular dichroism (CD) spectra of synthetic diplopyrone (**2**) in trifluoroethanol.

CONCLUSIONS

In summary, the first asymmetric total synthesis of the proposed structure of diplopyrone was achieved in 17 linear steps starting from commercially available stating material *cis*-1,4-butene-diol. Palladium-catalyzed epoxide ring opening reaction, iodine-catalyzed tandem isomerization followed by C-O and C-C bond formation reaction developed by our own group, asymmetric α-aminoxylation reaction, super-hydride reaction and Still-Gennari-(*Z*)-selective olefination reactions were used as key steps. It was found that there are serious discrepancies with the spectral values for the synthetic and natural samples, which suggest that the structure proposed for the natural product requires revision.

EXPERIMENTAL SECTION

General methods: Experiments which required an inert atmosphere were carried out under argon in flame-dried glassware. TBME and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled over KOH. Commercially available reagents were used as received. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with saturated aqueous $NaHCO_3$ solution (saturated aqueous NH_4Cl solution) was performed. Washing with brine, drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure followed by chromatography on a

silica gel column (60-120 mesh) with the indicated eluent furnished the corresponding products. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). High resolution mass spectra were run by the electron impact mode (ESIMS, 70 eV) or by the FAB mode (*m*-nitrobenzyl alcohol matrix), using an orbitrap mass analyzer. IR data were measured with oily films on NaCl plates (oils) or KBr pellets (solids). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1} and were measured at 29 °C or otherwise mentioned. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad.

((2*S*,3*S*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)oxiran-2-yl)methanol (9): L-(+)-DET (0.71 mL, 4.17 mmol) and $Ti(O^iPr)_4$ (1.08 mL, 3.68 mmol) were added subsequently to a stirred solution of flame dried 4Å powdered molecular sieve (4.9 g) in dry CH_2Cl_2 (65 mL) at −20 °C and stirred for 30 min. The corresponding *trans*-allyl alcohol (8.0 g, 24.5 mmol) in dry CH_2Cl_2 (15 mL) was added to the reaction mixture and stirred for another 30 min at the same temperature. TBHP (76.5 M in toluene, 5 mL, 49 mmol) was added and the resulting mixture was stirred at the same temperature for overnight. It was then warmed to 0 °C, quenched with water (21 mL), followed by 20% aqueous NaOH solution (5 mL) and stirred until clear separation of two layers occurred. It was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2 (3 × 100 mL) and washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:4) to get pure epoxy alcohol **9** (7.1 g, 85%) as a yellowish oil. R_f = 0.46 (SiO_2, 20% ethyl acetate in hexane). $[\alpha]_D^{29}$ = −7.1 (*c* = 0.05, $CHCl_3$); IR (neat) ν_{max} = 3349, 3071, 2932, 2860, 1468, 1428, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 4H), 7.46–7.36 (m, 6H), 3.95 (m, 1H), 3.88 (dd, *J* = 11.8, 3.0 Hz, 1H), 3.72 (dd, *J* = 12.1, 4.3 Hz, 1H), 3.63 (m, 1H), 3.17 (m, 1H), 3.08 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6, 135.5, 129.8, 127.7,

63.2, 61.2, 55.7, 55.6, 26.7, 19.2; HRMS (ESI): *m/z* calcd. for $C_{20}H_{26}O_3NaSi$ $[M + Na]^+$: 365.1543; found 365.1546.

(*E*)-Ethyl 3-((2*S*,3*S*)-3-((*tert*-butyldiphenylsilyloxy)methyl)oxiran-2-yl)acrylate (7): To a solution of oxalyl chloride (2.6 mL, 30.7 mmol) in CH_2Cl_2 (60 mL), was added DMSO (3.6 mL, 51.2 mmol) at –78 °C under nitrogen atmosphere and stirred for 20 min. A solution of epoxy alcohol **9** (7.0 g, 20.4 mmol) in CH_2Cl_2 (15 mL) was added and stirred for 45 min. Then triethylamine (11.3 mL, 81.9 mmol) was added, and the stirring continued for 20 min. The mixture was allowed to warm to 0 °C. After completion of reaction (as monitored by TLC), it was quenched with water (30 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extract was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude aldehyde was used for the next step immediately without further purification. To a stirred solution of the crude aldehyde in benzene (50 mL) was added ethoxycarbonylmethylene triphenylphosphorane (7.83 g, 22.5 mmol) at room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to afford the desired unsaturated ester compound **7** (7.4 g, 89%) as yellowish viscous liquid. R_f = 0.45 (SiO_2, 10% ethyl acetate in hexane); $[\alpha]_D^{29} = -14.2$ (*c* = 0.48, $CHCl_3$); IR (neat) ν_{max} = 3071, 2958, 2933, 2859, 1722, 1658, 1266, 1137, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4H), 7.47–7.37 (m, 6H), 6.66 (dd, *J* = 15.8, 7.2 Hz, 1H), 6.11 (d, *J* = 15.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 3.7 Hz, 2H), 3.36 (dd, *J* = 7.1, 1.6 Hz, 1H), 3.08 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 144.0, 135.5, 132.9, 129.8, 127.8, 124.0, 62.9, 60.8, 60.6, 53.8, 26.7, 19.2, 14.2; HRMS (ESI): *m/z* calcd. for $C_{24}H_{30}O_4NaSi$ $[M + Na]^+$: 433.1805; found 433.1819.

(4*S*,5*S*,*E*)-Ethyl-6-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-4-(4-methoxybenzyloxy)hex-2-enoate (10): To a solution of an α,β-unsaturated γ,δ-epoxy ester **7** (5.5 g, 13.4 mmol) in THF (15 mL) was added triphenyl borate (5.83 g, 20.1 mmol)), PMB-OH (6.3 mL, 60.3 mmol), and catalytic amount of $Pd(PPh_3)_4$ (1.34 g, 10 mol%) and the resulting reaction mixture was stirred at 0 °C for 2 h. After completion of the

reaction (as monitored by TLC), it was passed through a short silica gel column by the aid of ethyl acetate (100 mL) and the eluent was concentrated under reduced pressure to furnish the crude product. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:10) to afford **10** (6.1 g, 83%) as pale yellow oil. R_f = 0.52 (SiO_2, 20% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +5.3 (*c* = 0.92, $CHCl_3$); IR (neat) ν_{max} = 3517, 2933, 2859, 1719, 1514, 1250, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 4H), 7.45–7.35 (m, 6H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.94 (dd, *J* = 15.8, 6.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.11 (d, *J* = 15.8 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 3.73–3.67 (m, 3H), 2.50 (br s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 159.4, 144.8, 135.5, 132.9, 129.8, 129.6, 129.5, 127.7, 123.8, 113.8, 77.5, 73.5, 71.3, 63.8, 60.5, 55.2, 26.8, 19.2, 14.2; HRMS (ESI): *m/z* calcd. for $C_{32}H_{40}O_6NaSi$ $[M + Na]^+$: 571.2486; found 571.2479.

(4*S*,5*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)hex-2-ene-1,5-diol (6): DIBAL-*H* (25 wt% in toluene, 14.3 mL, 25.1 mmol) was added slowly to a stirred solution of *α,β*-unsaturated ester **10** (4.6 g, 8.4 mmol) in CH_2Cl_2 (30 mL) at −78 °C and stirring was continued for 30 min. After completion of the reaction, it was quenched by slow addition of methanol (5 mL) and followed by saturated aqueous solution of sodium potassium tartrate (50 mL), diluted with CH_2Cl_2 (150 mL) and allowed to stir at room temperature to get separated layers. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with brine (2 × 75 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product on silica gel column chromatography (ethyl acetate/hexane = 3:7) afforded aldehyde **6** (3.86 g, 91%) as light yellowish oil. R_f = 0.35 (SiO_2, 40% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +13.5 (*c* = 1.6, $CHCl_3$); IR (neat) ν_{max} = 3448, 2927, 2855, 1690, 1614, 1513, 1248, 1109, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 7.9 Hz, 1H), 7.66–7.60 (m, 4H), 7.47–7.35 (m, 6H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.79 (dd, *J* = 15.9, 5.8 Hz, 1H), 6.32 (dd, *J* = 15.9, 7.9 Hz, 1H), 4.56 (d J = 11.3 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.33 (m, 1H), 3.80 (s, 3H), 3.76–3.68 (m, 3H), 2.52 (br s, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.0, 159.4, 153.6, 135.5, 133.5, 132.8, 129.8, 129.6,

129.1, 127.7, 113.9, 77.5, 73.4, 71.7, 63.8, 55.2, 26.8, 19.1; HRMS (ESI): *m/z* calcd. for $C_{30}H_{36}O_5NaSi$ $[M + Na]^+$: 527.2224; found 527.2225.

(((2*S*,3*S*,6*S*)-6-Allyl-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)(*tert*-butyl) diphenylsilane (5): To a stirred solution of *δ*-hydroxy *α*,*β*-unsaturated aldehyde **6** (3.0 g, 5.9 mmol) and allyltrimethylsilane (2.37 mL, 14.8 mmol) in THF (25 mL) was added iodine (0.30 g, 1.2 mmol) at 0 °C and allowed to warm to room temperature. After completion of the reaction (as indicated by TLC), it was quenched with saturated solution of $Na_2S_2O_3$ (10 mL) and diluted with diethyl ether (40 mL). The aqueous layer was extracted with diethyl ether (2 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to obtain the cyclized product **5** (2.73 g, 87%) as light yellow oil. R_f = 0.45 (SiO_2, 10% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +21.0 (*c* = 1.2, $CHCl_3$); IR (neat) ν_{max} = 3100, 2922, 2853, 1731, 1640, 1513, 1464, 1429, 1360, 1247, 1120, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.73–7.66 (m, 4H), 7.42–7.34 (m, 6H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.91–5.89 (m, 2H), 5.79 (m, 1H), 5.07–4.99 (m, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.24 (m, 1H), 3.98–3.80 (m, 4H), 3.79 (s, 3H), 2.34 (m, 1H), 2.20 (m, 1H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 159.1, 135.6, 134.8, 134.5, 133.2, 130.8, 129.6, 129.3, 127.6, 124.3, 117.1, 113.6, 72.5, 71.9, 70.6, 67.8, 62.5, 55.2, 37.3, 26.9, 19.2. HRMS (ESI): *m/z* calcd. for $C_{33}H_{40}O_4SiNa$ $[M + Na]^+$: 551.2588, found 551.2601.

2-((2*S*,5*S*,6*S*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-5-(4-methoxybenzyloxy)-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde (11): To a stirred solution of cyclized compound **5** (2.4 g, 4.5 mmol) in 1,4-dioxane (25 mL), was added 2,6-lutidine (2.1 mL, 18.2 mmol), $NaIO_4$ (3.87 g, 18.2 mmol) and OsO_4 (1 M solution in toluene, 0.1 mL, 0.45 mmol) and stirring was continued at room temperature. After completion, the reaction was quenched with solid $NaHSO_3$ (15 mL). 1,4-Dioxane was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layer was washed with 1N HCl (2 × 50 mL) to remove excess 2,6-lutidine, dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:8) to give aldehyde **11** (1.75 g, 73%) as a light yellowish liquid. R_f = 0.40 (SiO_2, 20% ethyl acetate in hexane). $[\alpha]_D^{29}$ = +37.0 (*c* = 0.55, $CHCl_3$); IR (neat) ν_{max}= 3448, 3069, 2930, 2856, 1725, 1612, 1512, 1248, 1109, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 1.9 Hz, 1H), 7.68–7.65 (m, 4H), 7.45–7.32 (m, 6H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.99–5.83 (m, 2H), 4.78 (m, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.97–3.81 (m, 4H), 3.79 (s, 3H), 2.66 (ddd, *J* = 16.4, 8.7, 2.6 Hz, 1H), 2.46 (ddd, *J* = 16.4, 4.9, 1.9 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.5, 159.1, 135.6, 133.5, 131.7, 130.4, 129.7, 129.3, 127.7, 125.4, 113.7, 72.8, 70.6, 67.6 (d), 62.2, 55.2, 46.2, 26.8, 19.2; HRMS (ESI): *m/z* calcd. for $C_{32}H_{38}O_5NaSi$ $[M + Na]^+$: 553.2380; found 553.2410.

(*S*)-1-((2*R*,5*S*,6*S*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-5-(4-methoxybenzyloxy)-5,6-dihydro-2*H*-pyran-2-yl)ethane-1,2-diol (12): To a stirred solution of aldehyde **11** (1.0 g, 1.88 mmol) in dry DMSO (6 mL), nitroso benzene (0.20 g, 1.8 mmol) was added under nitrogen atmosphere and stirred for five minutes. *L*-proline (43 mg, 0.37 mmol) was added and stirred until color changed from green to deep orange. Then methanol (10 mL) was added to the reaction mixture and cooled to 0 °C. $NaBH_4$ (0.10 g, 2.8 mmol) was added portion wise and further stirred for 30 min. After complete disappearance of the starting material (as monitored by TLC), methanol was removed under reduced pressure and the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give deep orange colored syrup. The crude mass was dissolved in methanol and $CuSO_4.5H_2O$ (0.08 g, 0.3 mmol) was added at room temperature and stirred overnight. After removal of methanol from the reaction mixture, saturated aqueous solution of NH_4Cl (30 mL) was added and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using silica gel column chromatography (ethyl acetate/hexane = 1:1) to afford diol **12** (0.55 g, 62% over 2 steps) as a yellowish oil. R_f = 0.2 (SiO_2, 60% ethyl acetate in hexane). $[\alpha]_D^{29}$ = +31.4 (*c* = 0.4, $CHCl_3$); IR (neat) ν_{max} = 3446, 2931, 2857, 1612, 1512,

1248, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71–7.65 (m, 4H), 7.46–7.35 (m, 6H), 7.09 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 6.14–5.89 (m, 2H), 4.46 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 4.16 (m, 1H), 3.95–3.68 (m, 10H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.6, 133.3, 130.4, (130.2), 129.7, (129.6), 129.3, 127.7, 125.9, 125.4, 113.7, 74.2 (74.0), (73.5) 72.9, 72.4 (71.2), 70.4, 67.8 (67.4), 64.4, (63.2), 62.5, 55.2, 26.8, 19.1; HRMS (ESI): *m/z* calcd. for $C_{32}H_{40}O_6NaSi$ $[M + Na]^+$: 571.2486; found 571.2475.

***tert*-Butyl(((2*S*,3*S*,6*R*)-3-(4-methoxybenzyloxy)-6-((*S*)-oxiran-2-yl)-3,6-dihydro-2*H*-pyran-2-yl) methoxy)diphenylsilane (13):** Diol compound **12** (0.54 g, 0.99 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (60 wt% dispersion in mineral oil, 0.06 g, 1.50 mmol) in dry THF (15 mL) at 0 °C. After 30 min stirring, tosyl-imidazole (0.26 g, 1.2 mmol) was added to the reaction mixture and stirring was continued for another 1 h. The reaction was quenched by addition of water. The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:8) to afford required epoxy compound **13** (0.301 g, 58.1%) and the other isomer (0.129g, 24.9%) as a pale yellow liquid. R_f = 0.45 (SiO_2, 20% ethyl acetate in hexane). $[\alpha]_D^{29}$ = +61.2 (c = 0.4, $CHCl_3$); IR (neat) ν_{max} = 3450, 2925, 2854, 1736, 1613, 1512, 1248, 1109, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.65 (m, 4H), 7.46–7.32 (m, 6H), 7.16 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.07 (ddd, J = 10.1, 4.7, 2.1 Hz, 1H), 5.92 (dd, J = 10.4, 3.0 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.13 (m, 1H), 4.01–3.83 (m, 4H), 3.79 (s, 3H), 3.02 (m, 1H), 2.74 (dd, J = 4.9, 4.1 Hz, 1H), 2.60 (dd, J = 4.9, 2.6 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 135.6, 133.5, 129.6, 129.4, 128.8, 127.6, 127.2, 126.6, 113.7, 74.5, 72.5, 70.7, 67.3, 62.7, 55.2, 52.3, 44.8, 26.9, 19.2; HRMS (ESI): *m/z* calcd. for $C_{32}H_{38}O_5NaSi$ $[M + Na]^+$: 553.2380; found 553.2381.

(*S*)-1-((2*R*,5*S*,6*S*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-5-(4-methoxybenzyloxy)-5,6-dihydro-2*H*-pyran-2-yl)ethanol (14): To a stirred solution of epoxide **13** (0.37 g, 0.69 mmol) in dry THF (10

mL), was added super-hydride™ (1 M solution in THF, 3.49 mL, 3.49 mmol) dropwise at 0 °C. After completion of the reaction (as monitored by TLC), it was quenched by slow addition of water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:7) to afford compound **14** (0.29 g , 79%) as a yellowish oil. R_f = 0.5 (SiO_2, 30% ethyl acetate in hexane). $[\alpha]_D^{29}$ = +52.0 (*c* = 0.8, $CHCl_3$); IR (neat) ν_{max} = 3449, 2928, 2856, 1615, 1252, 1104, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4H), 7.45–7.35 (m, 6H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.05–5.92 (m, 2H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 3.94–3.89 (m, 3H), 3.86–3.80 (m, 2H), 3.78 (s, 3H), 3.71 (m, 1H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 135.6, 133.6, 130.3, 129.6, 129.3, 128.7, 127.6, 126.6, 113.7, 74.7, 74.4, 70.6, 69.4, 68.6, 61.6, 55.2, 26.9, 19.2, 18.0; HRMS (ESI): *m/z* calcd. for $C_{32}H_{40}O_5NaSi$ $[M + Na]^+$: 555.2537; found 555.2520.

(*S*)-(*S*)-1-((2*R*,5*S*,6*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5-((4-methoxybenzyl)oxy)-5,6-dihydro-2*H*-pyran-2-yl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (14a): To a solution of (*R*)-(–)-*α*-methoxy-*α*-trifluoromethylphenylacetic acid [(*R*)-MTPA] (17 mg, 74 μmol) in dry toluene (1.5 mL) at 0 °C were added Et_3N (20 μL, 150 μmol) and 2,4,6-$Cl_3C_6H_2COCl$ (30 μL, 112 μmol). The reaction mixture was stirred at room temperature for 30 min. Then the alcohol **14** (20 mg, 37 μmol) in toluene (0.5 mL) and DMAP (2 mg) were added to the reaction mixture at 0 °C. The resulting solution was stirred at room temperature for 3 h and the progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was directly concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to afford (*R*)-MTPA ester **14a** (19 mg, 70%) as a light yellowish liquid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.70–7.66 (m, 4H), 7.52–7.49 (m, 2H), 7.44–7.35 (m, 9H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.89 (ddd, *J* = 10.5, 4.7, 2.1 Hz, 1H), 5.62 (dd, *J* = 10.5, 2.4 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.03 (m, 1H), 3.86–3.79 (m, 3H), 3.78 (s, 3H), 3.73 (m, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 3.55 (s, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H).

(*R*)-(*S*)-1-((2*R*,5*S*,6*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5-((4-methoxybenzyl)oxy)-5,6-dihydro-2*H*-pyran-2-yl)ethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (14b): To a solution of (*S*)-(–)-*α*-methoxy-*α*-trifluoromethylphenylacetic acid [(*S*)-MTPA] (8 mg, 37 μmol) in dry toluene (1.0 mL) at 0 °C were added Et_3N (10 μL, 75 μmol) and 2,4,6-$Cl_3C_6H_2COCl$ (15 mL, 56 μmol), and the resulting mixture was stirred at room temperature for 30 min. Then the alcohol **14** (10 mg, 18 μmol) in toluene (0.5 mL) and DMAP (1 mg) were added to the reaction mixture at 0 °C. The resulting solution was stirred at room temperature for 3 h and the progress of the reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was directly concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to afford (*S*)-MTPA ester **14b** (11 mg, 75%) as a light yellowish liquid. R_f = 0.6 (SiO_2, 10% ethyl acetate in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.66 (m, 4H), 7.53–7.49 (m, 2H), 7.41–7.35 (m, 9H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.96 (ddd, *J* = 10.5, 4.2, 2.1 Hz, 1H), 5.84 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.11 (m, 1H), 3.90–3.80 (m, 3H), 3.79 (s, 3H), 3.60 (q, *J* = 7.2 Hz, 2H), 3.51 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.06 (s, 9H).

***tert*-Butyl(((2*S*,3*S*,6*R*)-6-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl)-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)diphenylsilane (15):** To a stirred solution of alcohol **14** (0.25 g, 0.47 mmol) in CH_2Cl_2 (10 mL) under nitrogen atmosphere, was added 2,6-lutidine (0.08 mL, 0.70 mmol) followed by TBSOTf (0.13 mL, 0.56 mmol) dropwise at 0 °C and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and washed with 1 N HCl (2 × 25 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under reduced pressure to obtain the crude product which on purification by silica gel column chromatography (ethyl acetate/hexane = 1:19) furnished the desired TBS-ether **15** (0.28 g, 93%) as a yellowish liquid. R_f = 0.35 (SiO_2, 5% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +93.0 (*c* = 0.55, $CHCl_3$); IR (neat) ν_{max}= 2930, 2853, 1725, 1615, 1400, 1255, 1084 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 4H), 7.44–7.33 (m, 6H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.17 (dd, *J* = 10.5, 2.9 Hz,

1H), 5.94 (ddd, *J* = 10.4, 4.6, 2.1 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 3.90 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.84–3.70 (m, 8H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.07 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 135.7, 133.6, 132.3, 130.8, 129.6, 129.4, 127.7, 124.2, 113.7, 76.6, 73.8, 70.4, 69.5, 67.5, 62.8, 55.3, 26.9, 25.8, 21.4, 19.2, 18.0, −4.2, −4.8; HRMS (ESI): *m/z* calcd. for $C_{38}H_{54}O_5NaSi_2$ $[M + Na]^+$: 669.3402; found 669.3429.

((2*S*,3*S*,6*R*)-6-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methanol (16): NH_4F (0.07 g, 1.85 mmol) was added to a stirred solution of **15** (0.20 g, 0.31 mmol) in anhydrous MeOH (6 mL) at room temperature. The reaction mixture was allowed to stir overnight. After complete consumption of stating material (monitored by TLC), MeOH was removed under vacuum and quenched by saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:6) to yield alcohol **16** (0.11 g, 85%) as a colorless liquid. R_f = 0.2 (SiO_2, 20% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +71.4 (*c* = 0.55, $CHCl_3$); IR (neat) ν_{max} = 3450, 2925, 2854, 1728, 1614, 1461, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.07 (ddd, *J* = 10.5, 4.1, 2.6 Hz, 1H), 5.97 (dd, *J* = 10.5, 2.6 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.19 (m, 1H), 4.10 (ddd, J = 8.7, 4.9, 3.9 Hz, 1H), 3.95–3.84 (m, 3H), 3.80 (s, 4H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 131.9, 130.1, 129.4, 123.6, 113.9, 76.5, 72.9, 70.2, 69.6, 68.5, 62.4, 55.3, 25.8, 21.2, 17.9, −4.3, −4.8; HRMS (ESI): *m/z* calcd. for $C_{22}H_{36}O_5NaSi$ $[M + Na]^+$: 431.2224; found 431.2225.

(*Z*)-Methyl-3-((2*S*,3*S*,6*R*)-6-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-((4-methoxybenzyl)oxy)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (4): IBX (0.15 g, 0.55 mmol) was added to a stirred solution of alcohol **16** (0.09 g, 0.22 mmol) in CH_3CN (9 mL) and refluxed for 3 h. After complete consumption of the starting material (as monitored by TLC), the reaction mixture was diluted with *tert*-butylmethyl ether

(30 mL) and the solid precipitates were filtered using Celite bed. The residue was washed with *tert*-butylmethyl ether (2 × 30 mL). The colorless filtrate was washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to get crude aldehyde as a yellow liquid which was directly used for the next reaction without further purification.

To a stirred suspension of NaH (60 wt% dispersion in mineral oil, 5 mg, 135 μmol) in THF (5 mL) at 0 °C under argon atmosphere, was added *bis*(2,2,2-trifluroethyl)methylphosphonate (43 mg, 135 μmol) and stirred for 30 min at the same temperature. The reaction mixture was cooled to −78 °C and a solution of crude aldehyde (50 mg, 123 μmol) in THF (2 mL) was added dropwise. After the mixture was stirred for 1 h, the reaction was quenched by slow addition of water (5 mL) at 0 °C and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:12) to obtain unsaturated ester **4** (44 mg, 78%) as a colorless liquid. R_f = 0.3 (SiO_2, 10% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +88.0 (*c* = 0.16, $CHCl_3$); IR (neat) ν_{max} = 2928, 2856, 1732, 1636, 1515, 1250, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.43 (dd, *J* = 11.9, 7.6 Hz, 1H), 6.19 (dd, *J* = 10.5, 3.5 Hz, 1H), 5.98 (ddd, *J* = 10.5, 4.6, 2.1 Hz, 1H), 5.91 (dd, *J* = 11.7, 1.4 Hz, 1H), 5.36 (ddd, *J* = 7.6, 3.2, 1.4 Hz, 1H), 4.49 (ABq, *J* = 11.7 Hz, $\Delta\nu$ = 17.4 Hz, 2H), 4.06 (m, 1H), 3.91–3.82 (m, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 1.19 (d, *J* = 5.8 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 159.1, 147.5, 131.2, 130.5, 129.4, 124.5, 120.2, 113.6, 76.6, 70.7, 69.9, 69.6, 69.0, 55.2, 51.3, 25.8, 21.3, 17.9, −4.3, −4.8; HRMS (ESI): *m/z* calcd. for $C_{25}H_{38}O_6NaSi$ $[M + Na]^+$: 485.2329; found 485.2344.

(4a*S*,6*R*,8a*S*)-6-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-6,8a-dihydropyrano[3,2-b]pyran-2(4a*H*)-one (17): To a stirred solution of compound **4** (35 mg, 75 μmol) in CH_2Cl_2 (5 mL) and pH =7 buffer (0.5 mL) was added DDQ (20 mg, 90 μmol) at 0 °C and allowed to stir at same temperature. After completion of the reaction (as monitored by TLC), it was quenched with saturated aqueous solution of $NaHCO_3$ (15 mL). Aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer

was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. As the product was unstable, we proceeded for next step without purification and characterization. PTSA (2 mg, 13.4 μmol) was added to a stirred solution of crude compound (23 mg, 67 μmol) dissolved in dry benzene (5 mL) at room temperature and stirred for 1 h. The reaction mixture was quenched by aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (2 × 15 mL) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 3:7) to obtain lactone **17** (20 mg, 86% over 2 steps) as a colorless liquid. R_f = 0.5 (SiO_2, 20% ethyl acetate in hexane); $[\alpha]_D^{29}$ = +41.0 (*c* = 0.19, $CHCl_3$); IR (neat) ν_{max} = 2926, 2854, 1732, 1463, 1371, 1253, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 10.0, 3.9 Hz, 1H), 6.23 (ddd, *J* = 10.5, 2.3, 1.3 Hz, 1H), 6.10 (dd, *J* = 10.0, 1.5 Hz, 1H), 6.00 (ddd, *J* = 10.5, 3.7, 2.3 Hz, 1H), 4.83 (m, 1H), 4.70 (m, 1H), 3.92 (m, 1H), 3.87 (q, *J* = 6.1 Hz, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 143.5, 132.0, 123.5, 122.4, 76.1, 70.2, 69.8, 63.7, 25.7, 20.7, 17.9, −4.3, −4.8; HRMS (ESI): *m/z* calcd. for $C_{16}H_{27}O_4Si$ $[M + H]^+$: 311.1673; found 311.1658.

(4a*S*,6*R*,8a*S*)-6-((*S*)-1-Hydroxyethyl)-6,8a-dihydropyrano[3,2-b]pyran-2(4a*H*)-one (2): To a stirred solution 17 (15 mg, 48 μmol) in dry THF (5 mL) in a polypropylene vial, was added HF.pyridine complex (70% solution, 0.02 mL) at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 12 h. After completion of the reaction (monitored by TLC), it was cautiously poured into saturated aqueous $NaHCO_3$ (5 mL), diluted with ethyl acetate (10 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (5 mL), water (5 mL), brine (5 mL) and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 3:7) to afford compound **2 (**8.5 mg, 90%**)** as a light yellowish liquid. R_f =0.3 (SiO_2, 40% ethyl acetate in hexane). $[\alpha]_D^{25}$ = +49.0 (*c* = 0.28, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ +67.6 (*c* = 0.25, $CHCl_3$)}; IR (neat) ν_{max} = 3418, 2922, 2853,

1716, 1633, 1461, 1377, 1256, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.88 (ddd, *J* = 10.0, 3.1, 1.0 Hz, 1H), 6.07 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.06 (td, *J* = 10.5, 1.6, 1.6 Hz, 1H), 6.04 (td, *J* = 10.5, 2.6, 2.6 Hz, 1H), 4.97 (m, *J* = 5.6, 2.6, 2.6, 1.6, 1.0 Hz, 1H), 4.92 (ddd, *J* = 5.6, 3.1, 1.6 Hz, 1H), 4.08 (ddt, *J* = 4.2, 2.6, 2.6, 1.6 Hz, 1H), 3.96 (dd, *J* = 6.4, 4.2 Hz, 1H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 144.2, 129.6, 124.7, 123.3, 74.8, 70.0, 69.7, 64.9, 18.7; HRMS (ESI): *m/z* calcd. for $C_{10}H_{13}O_4$ $[M + H]^+$: 197.0808; found 197.0798.

Acknowledgments. The authors thank Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as part of the XII Five Year plan programme under the title ORIGIN (CSC-0108). S.M. and S.K. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance in the form of fellowship.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005,** *22*, 369.

(2) (a) Jewers, J. R.; Davies, J. B.; Dougan, J.; Manchanda, A. H.; Blunden, G.; Kyi, A.; Wetchainan, S. *Phytochemistry* **1972**, *11*, 2025. (b) Hoffmann, H. M. R; Rabe, J. *Angew. Chem. Int. Ed.* **198**5, *24*, 94. (c) Pihie, A. H. L.; Stanslas, J.; Din, L. B. *Anticancer Res.* **1998**, *18*, 1739. (d) Hawariah, A.; Stanslas, J. *Anticancer Res.* **1998**, *18*, 4383. (e) Tanaka, S.; Yoichi, S.; Ao, L.; Matumoto, M.; Morimoto, K.; Akimoto, N.; Honda, G.; Tabata, M.; Oshima, T.; Masuda, T.; Asmawi, M. Z.; Ismail, Z.; Yusof, S. M.; Din, L. B.; Said, I. M. *Phytother. Res*. **2001**, *15*, 681.

(3) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X. Y.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2004**, *126*, 1038.

(4) (a) Tani, H.; Koshino, H.; Sakuno, E.; Cutler, H. G.; Nakajima, H. *J. Nat. Prod.* **2006**, *69*, 722. (b) Fukui, H.; Shiina, I. *Org. Lett.* **2008**, *10*, 3153.

(5) (a) Evidente, A.; Maddau, L.; Spanu, E.; Franceschini, A.; Lazzaroni, S; Motta, A. *J. Nat. Prod*. **2003**, *66*, 313. (b) Giorgio, E.; Maddau, L.; Spanu, E.; Evidente, A.; Rosini, C. *J. Org. Chem*. **2005**, *70*, 7.

(6) (a) Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron Lett.* **1978**, *19*, 69. (b) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099.

(7) (a) Mohapatra, D. K.; Bhimireddy, E.; Krishnarao, P. S.; Das, P. P.; Yadav, J. S. *Org. Lett*. **2011**, *13*, 744. (b) Yadav, J. S.; Pattanayak, M. R.; Das, P. P.; Mohapatra, D. K. *Org. Lett*. **2011**, *13*, 1710. (c) Mohapatra, D. K.; Maity, S.; Rao, T. S.; Yadav, J. S.; Sridhar, B. *Eur. J. Org. Chem*. **2013**, 2859. (d) Reddy, D. S.; Padhi, B.; Mohapatra, D. K. *J. Org. Chem.***2015**, *80*, 1365. (e) Padhi, B.; Reddy, D. S.; Mohapatra, D. K. *Eur. J. Org. Chem*. **2015**, 542. (f) Thirupathi, B.; Mohapatra, D. K. *Org. Biomol. Chem.* **2016**, *14*, 6212.

(8) Izzo, I.; Scioscia, M.; Gaudio, P. D.; Riccardis, F. D. *Tetrahedron Lett.* **2001**, *42*, 5421.

(9) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480.

(10) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem*. **1985**, *50*, 2198.

(11) Yu, X. -Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 750.

(12) Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. *Chem. Eur. J.* **2010**, *16*, 2072.

(13) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

(14) (a) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637. (b) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 10187. (c) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611. (d) Chacko, S.; Ramapanicker, R. *J. Org. Chem.* **2015**, *80*, 4776.

(15) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122.

(16) (a) Lei, X.; Jr. Porco, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 14790. (b) Clark, J. S.; Grainger, D. M.; Ehkirch, A. A. -C.; Blake, A. J.; Wilson C. *Org. Lett.* **2007**, *9*, 1033.

(17) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778. (c) Hoye, T. R.; Jeffrey, C. S.; Shao F. *Nature protocols* **2007**, *2*, 2451. (d) Altendorfer, M.; Raja, A.; Sasse, F.; Irschik, H.; Menche, D. *Org. Biomol. Chem.* **2013**, *11*, 2116.

(18) (a) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 3029. (c) Mohapatra, D. K.; Kanikarapu, S.; Naidu, P. R.; Yadav, J. S. *Tetrahedron Lett.* **2015**, *56*, 1041.

(19) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(20) (a) Jr. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73. (b) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (c) Dias, L. C.; Meira, P. R. R. *J. Org. Chem.* **2005**, *70*, 4762.

(21) (a) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021. (b) Sanchez, C. C.; Keck, G. E. *Org*. *Lett*. **2005**, *7*, 3053.

(22) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.