A facile approach for the construction of the oxetane ring from 5α-acyloxy-$\Delta^{4(20)}$-taxoids

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An oxetane ring can be constructed from 5α-acyloxy-$\Delta^{4(20)}$-taxoids. The facile intramolecular acyl migration from 5- to 20-position under slightly basic conditions enabled the construction of the oxetane ring in a convenient short cut, whereas the acyl migration from 2- to 20-position left the 2-hydroxyl accessible to a later benzoylation. An unexpected five-membered 4-*O*, 20-*O* sulfite ring was formed in the attempted construction of the oxetane ring with 5α-triflate as a leaving group. After the construction of the oxetane ring, treatment with strong base LiHMDS and acetyl chloride gave the expected 4-*O*-acetate while treatment with acetic anhydride and DMAP gave a 4-*O*-acetoacetate.

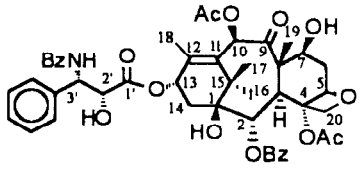
Keywords Taxoids, oxetane ring, intramolecular acyl migration, five-membered 4-*O*, 20-*O*-sulfite ring, unusual acylation

Introduction

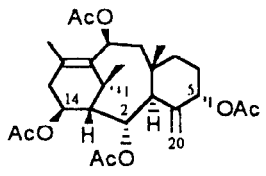
Paclitaxe (**1**)[1] has become famous for its unique anticancer mechanism, novel chemical structure and notable antitumor activity. It has been approved for clinical treatment of ovarian cancer and breast cancer respectively by FDA in 1992 and 1994. SAR studies disclosed that an oxetane ring is necessary for its antitumor activity.[2]

Sinenxan A (**2**) has been available as a biosynthetic taxane since 1992.[3] Taxinine (**3**) was separated from the needle of *Taxus X Media*. With these two 5α-acyloxyl-$\Delta^{4(20)}$-taxoids in hand, one of our efforts to use them as starting material in the search of anticancer agents is to construct the oxetane ring.

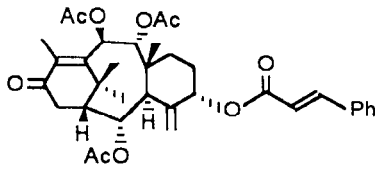
Scheme 1



Paclitaxel (1)



Sinenxan A (2)



Taxinine (3)

Results and discussion

Sinenxan A could be thoroughly hydrolyzed with methanolic potassium hydroxide to give tetraol **4** in which the 5α-OH is located in the more hindered position than the other hydroxyl groups. Therefore treatment of **4** with acetic anhydride under mild conditions yielded compound **5**, along with **2**. The $\Delta^{4(20)}$- double bond of **5** was dihydroxylated with a catalytic amount of OsO_4 and four equivalents of NMO, but the use of Na_2SO_3 during work-up produced a product **7** involving 2- to 20-Ac migration. When less basic reductive agent $NaHSO_3$ was used, the desired compound **6** was obtained in 86% yield. However, the construction of oxetane ring through

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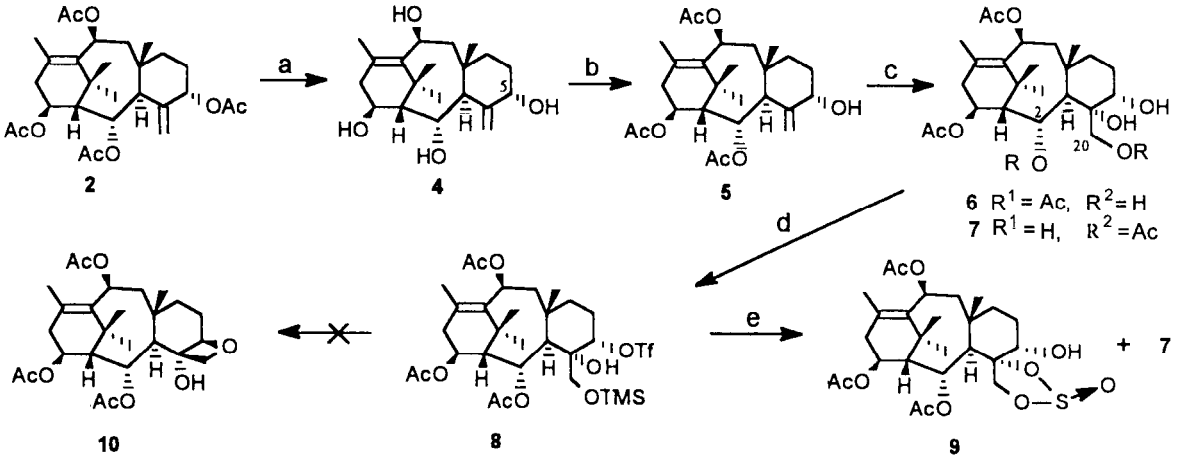
5-triflate **8** failed to afford the desired compound.[4] Two unexpected compounds **9** and **7** were isolated by acidic deprotection of 20-*O*-TMS with trace amount of camphorsulfonic acid followed by neutralization with saturated $NaHCO_3$ solution.



a) KOH, methanol, 60℃; b) acetic anhydride, pyridine, CH_2Cl_2, 25℃, 60% (two steps); c) OsO_4, NMO, 25℃, 4 days, 86%; d) TMSCl, pyridine, CH_2Cl_2, −5℃, then Tf_2O, −50℃, 4 h; e) camphorsulfonic acid, K_2CO_3, 25℃. **9**:8%, **7**:27% (two steps).

The similarity of the geminal coupling constant (7.8 Hz) of the 20-H to that of paclitaxel (8.4 Hz)[5a] aroused our interest. In comparison, ^2J of taxoids with a tetrahydrofuran ring at 2-, 3-, 4- and 20- is in the order of 10 Hz.[5b] X-ray crystallography of **9** disclosed the unique five-membered sulfite structure where the configuration of the sulfite sulfur was found to be *S* as shown in Fig. 1.

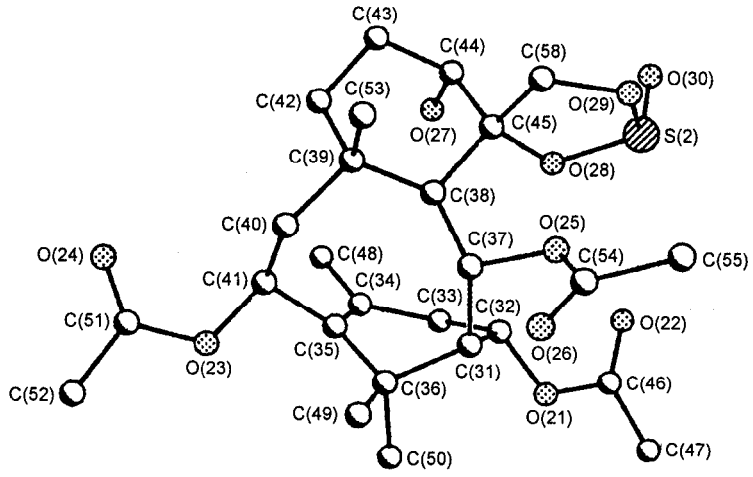


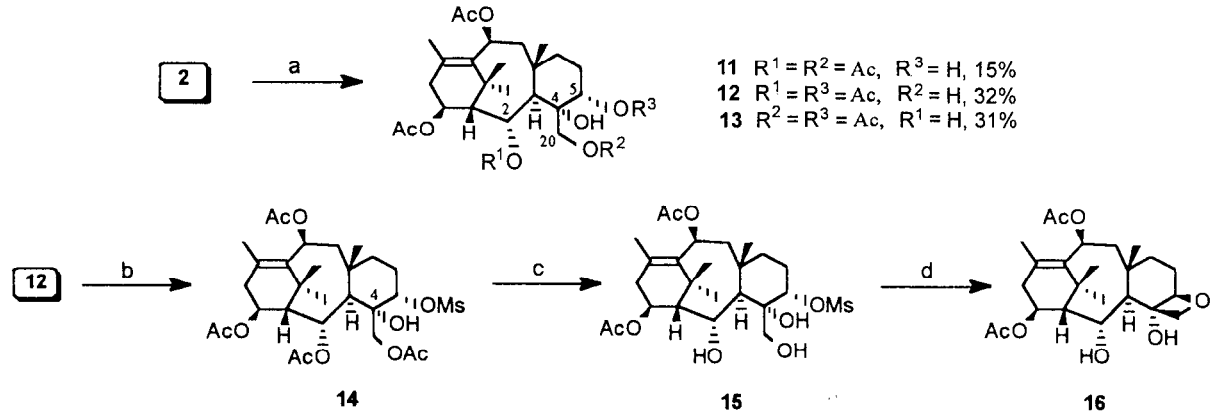
Fig. 1 Structure of compound **9** determined by X-ray crystallography.

Tf_2O was found not to contain $SOCl_2$ as an impurity, a suspected culprit for sulfite formation. Therefore the formation of the cyclic sulfite **9** from the triflate is rather baffling since it involves fission of the bond between CF_3- and $-SO_2$- and reduction of the sulfonate to the sulfite stage.

Another pathway to construct the oxetane ring was from direct osmylation of sinenxan A (Scheme 2).

Treatment of sinenxan A (**2**) with OsO_4 formed the 1:1 then the 2:1 osmate,[6] both tightly bound even under basic conditions, thus excluding the use of catalytic OsO_4 oxidation. Therefore an equimolar amount of OsO_4 was used without NMO for its oxidative regeneration . The 1:1 osmate thus formed was cleaved reductively with Na_2SO_3. This slightly basic medium again gave rise to the acyl migration, from 2- and 5-position to 20-OH, furnishing **12** and **13**, alongside of **11** as the unrearranged product. The formation of **12**, as the result of 5- to 20-migration, has to involve the intermediacy of 4-OAc since the 5-axial ester and 4-axial-CH_2OH are too far apart. This spatial disposition can be readily seen from the positive NOE between 20-proS and the angular Me protons. The newly discovered 5- to 20-acyl migration obviates the inconvenient protection and deprotection of 20-OH with a TMS group.[7]

Scheme 2



a) OsO_4, 25—30℃, 1 h, Na_2SO_3; b) MsCl, pyridine, 25℃, 60 h, 74%; c) K_2CO_3, methanol, 0℃, 15 min. d) DBU, toluene, 110℃, 1 h, 87% (two steps).

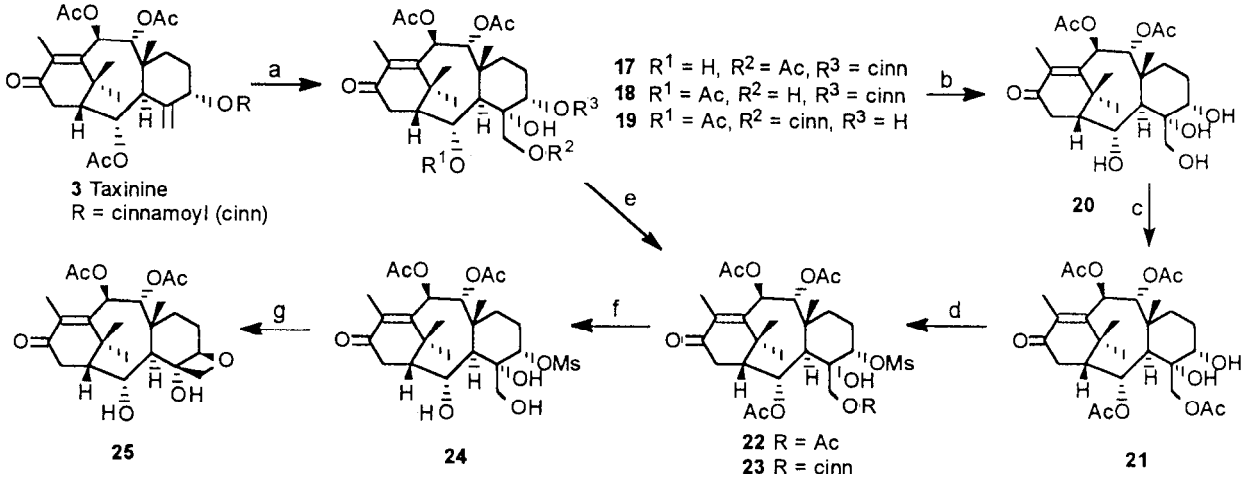
Conversion of the 5α-OH of compound **12** to its methanesulfonate **14** was uneventful since it is the only unhindered OH. This was followed by removal of the protective acyl group at the 20-position. It was fortunate indeed (*vide infra*) to have a simultaneous hydrolysis of the 2-ester (giving **15**) as the result of the facile 2- to 20-migration. Oxetane ring closure was accomplished in the usual way to give **16** by heating **15** with DBU.[8]

When the above method for construction of the oxetane ring was applied to taxinine (**3**) (Scheme 3), a similar result was obtained but in the osmylation-hydrolysis-migration procedures the ratio of 5-migrated product to 2-migrated product (1:4) was much lower than that from sinenxan A (1:1) (Scheme 2). This is reasonable since the cinnamoyl carbonyl is comparatively more reluctant to receive a nucleophile. To overcome the low yield caused by unsatisfactory migration, the compounds **17** and **18** were subjected to hydrolysis, then followed by careful reacetylation to afford **21** in 52% yield which served as an improved version of **19**. The target compound **25** was obtained from **19** or **21** using the similar strategy described in Scheme 3.

Because the 4-hydroxyl group of 4-deacetyl paclitaxel is located in a very hindered position, its reacetylation has to be effected under vigorous conditions and usually gives only moderate yields.[9] The attempted 4-acetylation of the compound **26**[10] derived from **2**, under similar forcing conditions, led to the formation of a 4-*O*-acetoacetate (**27**) as a major product (Scheme 4). With strong base to form its 4-oxide anion, the desired product **29** was obtained only in low yield, still accompanied with the formation of **27**.

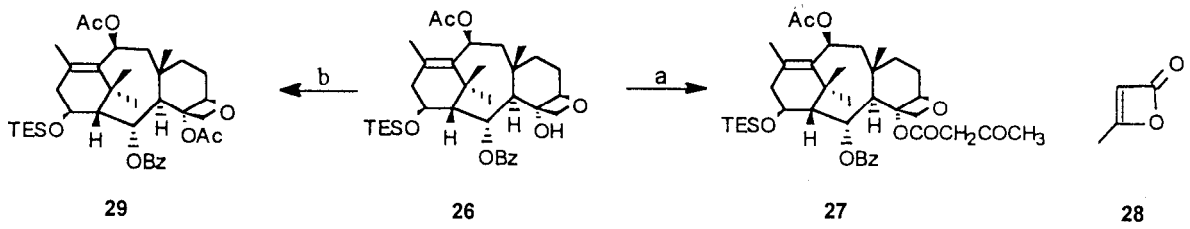
The formation of 4-*O*-acetoacetate is unusual. Evidently the 4-OH is too hindered to allow fruitful encounters with the bulky Ac_2O to form the 4-*O*-acetate. There must be a more reactive species which gives directly the acetoacetate. We would like to propose **28** as the less bulky reactive species, which is generated during the prolonged acetylation process. The involvement of **28** is strongly supported by the presence of the enolic form as the major isomer (ca. 60 %) in the acetoacetate (**27**).

Scheme 3



a) OsO_4, THF, 25℃, 14 h, Na_2SO_3, **17** 46%, **18** 26 %, **19** 12%; b) K_2CO_3, methanol, 0℃, 83%; c) acetic anhydride, pyridine, 25℃ , 48 h, 52%; d) MsCl, pyridine, 25℃, overnight, 83%; e) MsCl, pyridine, 25℃, 24 h, 72%; f) K_2CO_3, methanol, 0℃, 85%; g) DBU, toluene, 105℃, 1.5 h, 46%.

Scheme 4



a) Ac_2O, DMAP, 35 ℃, 5 h, 56%; b) LiHMDS, AcCl, 0℃, 1.5 h, 51%.

When **27** was dissolved in slightly acidic $CDCl_3$, a slow conversion of the enolic form to the keto form could be observed by ^1H NMR. This is indicative of the kinetically controlled acylation of **26** by some enolic acylating agent, here proposed as **28**. Diketene, an isomer of **28**, can be safely excluded as a likely acylating agent by having the *wrongly* disposed terminal double bond.

There is no satisfactory rationale for step-wise and site-specific *bis*-acetylation where one-step acylation by agent like **28** is not invoked. Further support for one-step acylation was furnished by the following experiment. A mixture of Ac_2O and DMAP was allowed to stand for one to two days, to which more than one equivalent of aniline was added all at once. The expected $PhNHCO\text{-}CH_2\text{-}COCH_3$ formed in trace amounts was not amenable to convenient separation or direct detection in the presence of acetanilide, the major product. It was derivatized by $H_2N\text{-}O\text{-}CH_2\text{-}COOH$ to give an oxime, which can be extracted into aqueous alkali, isolated and compared with an authentic specimen of $PhNH\text{-}CO\text{-}CH_2C(CH_3)=N\text{-}O\text{-}CH_2\text{-}COOH$ (TLC and ^1H NMR).

Conclusions

A facile approach was established for the construction of the oxetane ring using an intramolecularly available acyl group for the protection of 20-OH by an unexpected 5- to 20-migration. This "internal protection" obviates the inconvenient protection and deprotection of 20-OH. It is promising to be a general procedure for the construction of the oxetane ring from 5α-acyloxy-$\Delta^{4(20)}$-taxoids. The simultaneous removal of the 2-acyl group

accompanied by hydrolysis of 20-ester facilitated 2-modification, for example, 2-benzoylation as a mimicry of paclitaxel, where the 2-benzoate is another essential contributor to activity. This avoids the undesirable hydrolysis step which can hardly be accomplished without endangering other ester groups.

The unusual one step acylation of 4-OH to give 4-*O*-acetoacetate was observed. The possible mechanism was confirmed by ^{1}H NMR and chemical studies.

Experimental

General procedures

All reactions were carried out under nitrogen atmosphere. Anhydrous THF was freshly distilled from $LiAlH_4$. All solutions used in the workup procedures are saturated unless otherwise specified. Silica gel (180—200 mesh) was used for column chromatography. NMR spectra were recorded on Bruker AM500 and ARX400 instruments and tetramethylsilane was used as internal reference. Mass spetra were obtained on a Jeol JMS-SX102 mass spectrometer (matrix: *m*-NBA *m*-nitro benzyl alcohol). High resolution mass spectra were recorded on a Bruker FTMS-APEX^{TM} II mass spectrometer (matrix: *m*-NBA). Melting points are uncorrected.

The structure of sinenxan A was established by X-ray crystallography and the assignment of ^{1}H signals was firmly ascertained by 2D NMR. The characteristic splitting patterns of individual groups were served as a convenient point of departure for following changes of functionalities.

Preparation of compound **5** A solution of **2** (22.95 g, 45.50 mmol) in methanol (200 mL) was treated with KOH (12.76 g, 0.228 mol, in 18 mL of H_2O) at 60℃ for 7 h. After solvent was removed, the residue was dissolved in pyridine (20 mL) and acetic anhydride (46.5 mL, 0.492 mol) divided in four portions was added in a reaction period of 8 days at 25℃, then the excess acetic anhydride was decomposed by addition of methanol (50 mL). After removal of methanol, the mixture was poured into ice-water (400 mL), extracted with ethyl acetate (4 × 150 mL). The combined extracts were washed with dilute HCl (10% HCl in 1000 mL of H_2O), brine, dried over Na_2SO_4, concentrated and the residue was chromatographed (petroleum ether/ethyl acetate 3.5:1) to give recovered **2** (16.45 g, 72%) and **5** (3.57 g, 60% based on recovery of starting material). **5**: mp 71—73℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11(dd, J = 12.0, 5.6 Hz, 1H, 10-H), 5.34(dd, J = 6.3, 2.3 Hz, 1H, 2-H), 5.10 (s, 1H, 20-H), 5.03(dd, J = 9.3, 4.6 Hz, 1H, 14-H), 4.78(t, J = 1.5 Hz, 1H, 20-H), 4.18(t, J = 2.7 Hz, 1H, 5-H), 2.77(dd, J = 19.0, 9.3 Hz, 1H, 13-H), 2.37—2.29(m, 2H, 13-H and 9-H), 2.21 (d, J = 6.2 Hz, 1H, 3-H), 2.09(m, 1H, 6-H), 2.10(s, 3H, Ac), 2.08(s, 3H, 18-CH_3), 2.04 (s, 3H, Ac), 2.02(s, 3H, Ac), 1.84(d, J = 2.1 Hz, 1H, 1-H), 1.69—1.80(m, 2H, 6-H and 7-H), 1.65(s, 3H, 16-CH_3), 1.59(dd, J = 14.8, 5.5 Hz, 1H, 9-H), 1.08—1.19(m, 1H, 7-H), 1.11(s, 3H, 17-CH_3), 0.81(s, 3H, 19-CH_3). Anal. $C_{26}H_{38}O_7$. Calcd: C, 67.51; H, 8.28. Found: C, 67.80; H, 8.41.

Preparation of compound **6** A solution of **5** (700 mg, 1.513 mmol), NMO monohydrate (850 mg, 6.289 mmol) in a mixed solvent (THF 200 mL, acetone 30 mL, H_2O 6 mL) was treated with OsO_4 aqueous solution (4%, 0.9 mL, 0.146 mmol) at 25℃ for 4 days, then aqueous $NaHSO_3$ was added. After being concentrated, the residue was taken up by ethyl acetate and the organic phase was washed successively with 1 N HCl, aqueous $NaHCO_3$ solution, aqueous $NaHSO_3$ solution, brine, dried (Na_2SO_4) and concentrated to give crude product which was purified by column chromatography to yield product **6** as a white powder (643 mg, 86%). mp 179—182℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.03(dd, J = 12.1, 5.5 Hz, 1H, 10-H), 5.64(dd, J = 9.3, 4.7 Hz, 1H, 14-H), 5.33(dd, J = 5.4, 2.2 Hz, 1H, 2-H), 3.75(t, J = 2.7 Hz, 1H, 5-H), 3.51(d, J = 10.8 Hz, 1H, 20-H), 3.48 (d, J = 10.8 Hz, 1H, 20-H), 2.68(d, J = 5.4 Hz, 1H, 3-H), 2.63(dd, J = 18.9, 9.3 Hz, 1H, 13-H), 2.52(dd, J = 18.9, 4.7 Hz, 1H, 13-H), 2.25 (dd, J = 14.9, 12.3 Hz, 1H, 9-H), 2.13(s, 3H, Ac), 2.05(s, 3H, 18-CH_3), 2.04(s, 3H, Ac), 2.03(s, 3H, Ac), 2.04—1.96(m, 1H, 6-H), 1.80—1.72(m, 2H, 6-H and 7-H), 1.76(d, J = 2.2 Hz, 1H, 1-H), 1.63(s, 3H, 16-CH_3), 1.42(dd, J = 14.9, 5.5 Hz, 1H, 9-H), 1.13(s, 3H, 17-CH_3), 1.01—1.07(m, 1H, 7-H), 0.76(s, 3H, 19-CH_3). FAB MS m/z: 497($M+H^+$). HR ESI MS Calcd. for $C_{26}H_{40}O_9$($M+H^+$): 497.2751. Found: 497.2775.

Preparation of compound **8** To a solution of **6**

(105 mg, 0.211 mmol) and pyridine (300 mg, 3.793 mmol) in CH_2Cl_2(3 mL) was added trimethylsilyl chloride (TMSCl, 118 mg, 1.086 mmol) at −5℃ and the reaction mixture was stirred at −5℃ for 20 min, then the solvent was removed *in vacuo* and the residue was redissolved in CH_2Cl_2. This solution was cooled to −50 to −60℃ and *i*-Pr_2NEt (480 mg, 3.714 mmol) and triflic anhydride (Tf_2O, 531 mg, 1.882 mmol) were added. The resulting mixture was stirred for 4 h when the temperature was allowed to warm-up to room temperature, then poured into a mixture of ice-water/ether/$NaHCO_3$ solution. The organic layer was separated and the water layer was extracted with ether. The combined organic layers were washed with dilute HCl (3 N, 3 mL in 50 mL of H_2O), aqueous $NaHCO_3$, brine and dried over Na_2SO_4. After concentration, the crude was passed through a silica gel column, which was eluted quickly with petroleum ether/ethyl acetate (3:1) to give impure product (210 mg) which was taken to the next step without further purification. ^1H NMR (500 MHz, $CDCl_3$): δ6.03(dd, *J* = 12.2, 5.3Hz, 1H, 10-H), 5.72 (dd, *J* = 9.4, 3.8 Hz, 1H, 14-H), 5.27(dd, *J* = 4.9, 2.4 Hz, 1H, 2-H), 4.19(s, 1H, 5-H), 3.65 (d, *J* = 10.3 Hz, 1H, 20-H), 3.37(d, *J* = 10.3 Hz, 1H, 20-H), 3.10(dd, *J* = 19.6, 9.4 Hz, 1H, 13-H), 2.60(d, *J* = 4.9 Hz, 1H, 3-H), 2.40(br. d, *J* = 19.6 Hz, 1H, 13-H), 2.27(dd, *J* = 15.2, 12.2 Hz, 1H, 9-H), 2.09(s, 3H, Ac), 2.04(s, 3H, Ac), 2.03(s, 3H, 18-CH_3), 2.01(s, 3H, Ac), 2.00—1.82(m, 3H, 2 × 6-H and 7-H), 1.65(d, *J* = 2.4 Hz, 1H, 1-H), 1.60(s, 3H, 16-CH_3), 1.41 (dd, *J* = 15.2, 5.4 Hz, 1H, 9-H), 1.15(d, *J* = 11.6 Hz, 1H, 7-H), 1.11(s, 3H, 17-CH_3), 0.79 (s, 3H, 19-CH_3).

Compounds **7** *and* **9** A solution of **8** (210 mg) from the above step in methanol (5 mL) was treated with a trace amount of camphorsulfonic acid at 25℃ until the starting material disappeared, then one drop of $NaHCO_3$ solution was added and the solvent was removed *in vacuo*. The residue was taken up with ether, washed with brine, dried over Na_2SO_4, concentrated and the residue was chromatographed (petroleum ether/ethyl acetate 1.8:1 to 1:1) to yield **7** (31 mg, 27 %), and **9** (10 mg, 8%). **7**: mp 91—94℃; ^1H NMR (500 MHz, $CDCl_3$): δ 6.01(dd, *J* = 12.2, 5.5 Hz, 1H, 10-H), 5.63(t, *J* = 7.1 Hz, 1H, 14-H), 4.81(d, *J* = 11.5 Hz, 1H, 20-H), 4.38(d, *J* = 11.5 Hz, 1H, 20-H), 4.07(dd, *J* = 5.2, 2.3 Hz, 1H, 2-H), 2.59 (d, *J* = 7.1 Hz, 2H, 13-H), 2.41(d, *J* = 5.2 Hz, 1H, 3-H), 2.18(dd, *J* = 14.7, 12.3 Hz, 1H, 9-H), 2.08(s, 3H, Ac), 2.07(s, 3H, Ac), 2.04(s, 3H, 18-CH_3), 2.02(s, 3H, Ac), 1.97(dd, *J* = 10.5, 5.8 Hz, 1H, 6-H), 1.89(d, *J* = 2.3 Hz, 1H, 1-H), 1.71—1.81(m, 2H, 6-H and 7-H), 1.54(s, 3H, 16-CH_3), 1.37(dd, *J* = 14.7, 5.4 Hz, 1H, 9-H), 1.13(s, 3H, 17-CH_3), 1.03(br. d, *J* = 13.0 Hz, 1H, 7-H), 0.91(s, 3H, 19-CH_3). HR ESI MS Calcd. for $C_{26}H_{40}O_9$ ($M + Na^+$): 519.2570. Found: 519.2601. **9**: ^1H NMR (500 MHz, $CDCl_3$): δ 6.06 (dd, *J* = 12.1, 5.4 Hz, 1H, 10-H), 5.63(dd, *J* = 9.5, 4.1 Hz, 1H, 14-H), 5.30(dd, *J* = 4.9, 2.2 Hz, 1H, 2-H), 4.31(d, *J* = 7.8 Hz, 1H, 20-H), 4.24(d, *J* = 7.8 Hz, 1H, 20-H), 4.08(br. s, 1H, 5-H), 3.02(d, *J* = 4.9 Hz, 1H, 3-H), 2.68(dd, *J* = 19.2, 9.5 Hz, 1H, 13-H), 2.48(br.d, *J* = 19.2 Hz, 1H, 13-H), 2.29(dd, *J* = 14.0, 11.3 Hz, 1H, 9-H), 2.10—2.05(m, 1H, 6-H), 2.06(s, 3H, Ac), 2.05(s, 3H, 18-CH_3), 2.04(s, 3H, Ac), 2.02 (s, 3H, Ac), 1.88—1.94(m, 1H, 6-H), 1.76(s, 1H, 1-H), 1.66—1.74(m, 1H, 7-H), 1.63(s, 3H, 16-CH_3), 1.45(dd, *J* = 14.9, 5.3 Hz, 1H, 9-H), 1.12(s, 3H, 17-CH_3), 1.11—1.07(m, 1H, 7-H), 0.77(s, 1H, 19-CH_3).

Preparation of compounds **11**, **12** *and* **13** To a solution of **2** (800 mg, 1.585 mmol) in THF (40 mL) was added OsO_4 water solution (4%, 10.24 mL, 1.649 mmol, diluted in 120 mL of THF) in a period of 1 h. The solution was stirred at 25—30℃ for 4 h. Na_2SO_3 (1.6 g, 12.7 mmol) was dissolved in water and added to the stirred reaction mixture. After 6 h, another portion of Na_2SO_3(0.8 g, 6.35 mmol) was added and the mixture was stirred for 4 more hours, then neutralized with dilute HCl (10%) and concentrated. The ethyl acetate extracts (5 × 20 mL) of the residue were washed with water, dried over Na_2SO_4, concentrated and the residue was chromatographed (petroleum ether/acetone 9:1 to 5:1) to give **11** (0.13 g, 15 %), **12** (0.28 g, 32 %), **13** (0.26 g, 31 %). **11**: mp 168—170℃; ^1H NMR (400 MHz, $CDCl_3$): δ 6.00(dd, *J* = 12.1, 5.5 Hz, 1H, 10-H), 5.61(dd, *J* = 9.0, 4.6 Hz, 1H, 14-H), 5.32(dd, *J* = 5.2, 2.2 Hz, 1H, 2-H), 5.19(br.s, 1H, 5-H), 3.52(s, 2H, 2 × 20-H), 2.67(dd, *J* = 19.1, 9.0 Hz, 1H, 13-H), 2.57(dd, *J* = 19.1, 4.6 Hz, 1H, 13-H), 2.55(d, *J* = 5.1

Hz, 1H, 3-H), 2.29(dd, J = 14.9, 12.3 Hz, 1H, 9-H), 2.17(s, 3H, Ac), 2.13(s, 3H, Ac), 2.10 (s, 3H, 18-CH_3), 2.04(s, 3H, Ac), 2.01(s, 3H, Ac), 1.90—1.82(m, 2H, 6-H), 1.79(d, J = 2.1 Hz, 1H, 1-H), 1.68—1.76(m, 1H, 7-H), 1.62 (s, 3H, 16-CH_3), 1.44(dd, J = 14.9, 5.4 Hz, 1H, 9-H), 1.12(s, 3H, 17-CH_3), 1.04—1.11(m, 1H, 7-H), 0.79(s, 3H, 19-CH_3). HR ESI MS Calcd. for $C_{28}H_{42}O_{10}$(M + Na^+): 561.2676. Found: 561.2695. **12**: mp 67—70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04(dd, J = 12.2, 5.5 Hz, 1H, 10-H), 5.68(dd, J = 9.4, 4.6 Hz, 1H, 14-H), 5.33(dd, J = 5.2, 2.2 Hz, 1H, 2-H), 4.44(d, J = 11.9 Hz, 1H, 20-H), 4.08(d, J = 11.9 Hz, 1H, 20-H), 3.86(t, J = 2.7 Hz, 1H, 5-H), 2.70(d, J = 5.2 Hz, 1H, 3-H), 2.62(dd, J = 19.1, 8.2 Hz, 1H, 13-H), 2.49(br. d, J = 19.1 Hz, 1H, 13-H), 2.26(dd, J = 14.9, 12.2 Hz, 1H, 9-H), 2.19(s, 3H, Ac), 2.09(s, 3H, Ac), 2.05(s, 3H, 18-CH_3), 2.05(s, 3H, Ac), 2.02(s, 3H, Ac), 2.02—1.97(m, 1H, 6-H), 1.78 (d, J = 2.2 Hz, 1H, 1-H), 1.85—1.73(m, 2H, 6-H and 7-H), 1.63(s, 3H, 16-CH_3), 1.44(dd, J = 14.9, 5.4 Hz, 1H, 9-H), 1.12(s, 3H, 17-CH_3), 1.06(m, 1H, 7-H), 0.83(s, 3H, 19-CH_3). FAB MS m/z: 537 (M + H^+); HR ESI MS Calcd. for $C_{28}H_{42}O_{10}$(M + Na^+): 561.2676. Found: 561.2675. **13**: mp 154—156 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99(dd, J = 12.2, 5.4 Hz, 1H, 10-H), 5.72(dd, J = 7.6, 6.2 Hz, 1H, 14-H), 5.06(d, J = 3.1 Hz, 1H, 5-H), 4.85(d, J = 11.3 Hz, 1H, 20-H), 4.46 (d, J = 11.3 Hz, 1H, 20-H), 4.12—4.01(m, 1H, 2-H), 4.00(s, 1H, OH), 3.06(br. s, 1H, OH), 2.58(br. d, J = 7.7 Hz, 2H, 2 × 13-H), 2.24(dd, J = 14.8, 12.2 Hz, 1H, 9-H), 2.21(d, J = 4.2 Hz, 1H, 3-H), 2.17(s, 3H, Ac), 2.13(s, 3H, Ac), 2.10(s, 3H, Ac), 2.06(s, 3H, 18-CH_3), 2.05 (s, 3H, Ac), 1.92—1.82(m, 3H, 2 × 6-H and 1-H), 1.77—1.66(m, 1H, 7-H), 1.54(s, 3H, 16-CH_3), 1.41(dd, J = 14.8, 5.4 Hz, 1H, 9-H), 1.22 —1.14(m, 1 H, 7-H), 1.13(s, 3H, 17-CH_3), 0.96 (s, 3H, 19-CH_3). HR ESI MS Calcd. for $C_{28}H_{42}O_{10}$ (M + Na^+): 561.2676. Found: 561.2689.

Preparation of compound **14** A solution of **12** (260 mg, 0.483 mmol) in pyridine (6 mL) was treated with methanesulfonyl chloride (150 mL, 1.941 mmol) at room temperature for 60 h, then poured into ice-water (50 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with dilute HCl (1N, 60 mL), brine and dried over Na_2SO_4, concentrated and the residue was chromatographed to yield product (220 mg, 74%) as a white solid, mp 199—202℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03(dd, J = 12.1, 5.5 Hz, 1H, 10-H), 5.67(dd, J = 9.3, 4.4 Hz, 1H, 14-H), 5.34(dd, J = 4.9, 2.1 Hz, 1H, 2-H), 4.85(s, 1H, 5-H), 4.65 (d, J = 12.2 Hz, 1H, 20-H), 3.99(d, J = 12.2 Hz, 1H, 20-H), 3.09(s, 3H, -SO_2CH_3), 2.66(dd, J = 18.7, 9.3 Hz, 1H, 13-H), 2.62(d, J = 4.9 Hz, 1H, 3-H), 2.50(dd, J = 18.7, 4.4 Hz, 1H, 13-H), 2.27(dd, J = 14.8, 12.2 Hz, 1H, 9-H), 2.23(s, 3H, Ac), 2.10(s, 3H, Ac), 2.08(s, 3H, 18-CH_3), 2.05(s, 3H, Ac), 2.04(s, 3H, Ac), 2.03 —1.91(m, 3H, 2 × 6-H and 7-H), 1.79(d, J = 2.1 Hz, 1H, 1-H), 1.63(s, 3H, 16-CH_3), 1.49(dd, J = 14.8, 5.5 Hz, 1H, 9-H), 1.28—1.22(m, 1H, 7-H), 1.12(s, 3H, 17-CH_3), 0.86(s, 3H, 19-CH_3). FAB MS m/z: 617(M + H^+); HR ESI MS Calcd. for $C_{29}H_{44}O_{12}S$(M + Na^+) 639.2451. Found: 639.2481.

Preparation of compound **16** A solution of **14** (300 mg, 0.486 mmol) in methanol (30 mL) was treated with K_2CO_3 (134 mg in 2 mL of H_2O, 0.970 mmol) at 0℃ for 15 min, then dilute HCl (1 N, 1 mL) was added, and the mixture was concentrated. The residue was taken up with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated to give crude **15**, which was taken to the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99(dd, J = 12.1, 5.4 Hz, 1H, 10-H), 5.65(dd, J = 8.9, 4.9 Hz, 1H, 14-H), 4.72(d, J = 2.5 Hz, 1H, 5-H), 4.24(d, J = 11.4 Hz, 1H, 20-H), 4.08(dd, J = 5.2, 2.2 Hz, 1H, 2-H), 3.53(d, J = 11.4 Hz, 1H, 20-H), 3.08(s, 3H, -SO_2CH_3), 2.64—2.60 (m, 2H, 13-H), 2.37(d, J = 5.2 Hz, 1H, 3-H), 2.17(m, 1H, 9-H), 2.16(s, 3H, 18-CH_3), 2.06 (s, 3H, Ac), 2.02(s, 3H, Ac), 2.00—1.88(m, 3H, 2 × 6-H and 7-H), 1.84(d, J = 2.2 Hz, 1H, 1-H), 1.51(s, 3H, 16-CH_3), 1.41(dd, J = 14.9, 5.4 Hz, 1H, 9-H), 1.21—1.16(m, 1H, 7-H), 1.12(s, 3H, 17-CH_3), 0.88(s, 3H, 19-CH_3). FAB MS m/z: 533 (M + H^+).

To a solution of **15** in toluene (20 mL) was added DBU (150 mg, 0.970 mmol) and the reaction mixture

was stirred at 110℃ for 1 h, then cooled to room temperature, applied directly to column chromatography (petroleum ether/ethyl acetate 3:7) to yield product **16** as a white solid (185 mg, 87% from 14), mp 162—164℃. ^{1}H NMR (400 MHz, acetone-d_6): δ 5.95(dd, J = 12.4, 5.5 Hz, 1H, 10-H), 5.60(dd, J = 9.1, 4.8 Hz, 1H, 14-H), 4.64(dd, J = 8.9, 2,6 Hz, 1H, 5-H), 4.59(d, J = 8.0 Hz, 1H, 20-H), 4.30 (d, J = 8.0Hz, 1H, 20-H), 4.08(dd, J = 5.5, 2.8 Hz, 1H, 2-H), 2.85(d, J = 5.5Hz, 1H, 3-H), 2.57(dd, J = 18.9, 9.1 Hz, 1H, 13-H), 2.47(dd, J = 18.9, 4.8 Hz, 1H, 13-H), 2.33(dd, J = 14.7, 12.4 Hz, 1H, 9-H), 2.09(s, 3H, Ac), 2.00(s, 18-CH_3), 1.88(s, 3H, Ac), 1.88—1.85(m, 2H, 6-H), 1.74(d, J = 5.4 Hz, 1H, 1-H), 1.71—1.60 (m, 1H, 7-H), 1.58(s, 1H, 19-CH_3), 1.45—1.51 (m, 2H, 9-H and 7-H), 1.32(s, 3H, 17-CH_3), 1.13(s, 3H, 16-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 170.0, 135.9, 134.4, 87.7, 82.2, 76.8, 70.6, 70.3, 70.2, 61.2, 47.8, 45.2, 37.8, 37.6, 36.3, 35.8, 31.9, 27.4, 25.8, 21.9, 21.6, 21.3, 20.9; HR FAB MS Calcd. for $C_{24}H_{36}O_7$ ($M+H^+$): 437.2534, Found: 437.2539.

Prepatation of compounds **17**, **18** *and* **19** A solution of **3** (66 mg, 0.109 mmol) in THF (5 mL) was treated with aqueous OsO_4 (4%, 0.70 mL, 0.109 mmol) at 25℃ for 14 h, then aqueous Na_2SO_3 (5%, 1 mL, 0.397 mmol) was added and stirred at 25℃ for 2 h. The mixture was neutralized with HCl (5%) and concentrated *in vacuo*. The residue was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and the residue was purified by preparative TLC (silica gel, CH_2Cl_2/CH_3OH 35:1) to give **17** (32 mg, 46%), **18** (18 mg, 26%), and **19** (8 mg, 12%).

17: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75—7.64(m, 3H, COCH = CHPh and Ph-H), 7.47—7.38(m, 3H, Ph-H), 6.47(d, J = 15.9 Hz, 1H, COCH = C*H*Ph), 6.00(d, J = 10.3 Hz, 1H, 10-H), 5.75(d, J = 10.3 Hz, 1H, 9-H), 5.13(t, J = 3.0 Hz, 1H, 5-H), 4.80(d, J = 11.4 Hz, 1H, 20-H), 4.55(d, J = 11.4 Hz, 1H, 20-H), 4.23(br. s, 1H, 2-H), 4.07(br. d, J = 11.0 Hz, 1H, 2-OH), 3.28(s, 1H, 4-OH), 3.03(d, J = 19.9 Hz, 1H, 14-H), 2.73(dd, J = 19.9, 6.7 Hz, 1H, 14-H), 2.69 (d, J = 4.4 Hz, 1H, 3-H), 2.34(s, 3H, Ac), 2.30 (dd, J = 6.7, 1.7 Hz, 1H, 1-H), 2.15(s, 3H, Ac), 2.09(s, 3H, Ac), 2.05(s, 3H, 18-CH_3), 1.92—1.86(m, 2H), 1.76(dt, J = 13.6, 3.0 Hz, 1H, 6-H), 1.68(s, 3H, 16-CH_3), 1.68—1.59(m, 1H), 1.17(s, 3H, 17-CH_3), 0.99(s, 3H, 19-CH_3).

18: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73—7.62(m, 3H, COCH = CHPh and Ph-H), 7.44—7.35(m, 3H, Ph-H), 6.48(d, J = 15.9 Hz, 1H, COCH = C*H*Ph), 6.02(d, J = 10.3 Hz, 1H, 10-H), 5.78(d, J = 10.3 Hz, 1H, 9-H), 5.56(dd, J = 5.0, 2.1 Hz, 1H, 2-H), 5.15(t, J = 3.0 Hz, 1H, 5-H), 4.12(d, J = 11.4 Hz, 1H, 20-H), 3.78 (d, J = 11.4 Hz, 1H, 20-H), 3.03(d, J = 19.8 Hz, 1H, 14-H), 2.73(dd, J = 19.8, 6.7 Hz, 1H, 14-H), 2.65(d, J = 5.0 Hz, 1H, 3-H), 2.30(s, 3H, Ac), 2.25(dd, J = 6.7, 1.7Hz, 1H, 1-H), 2.12(s, 3H, Ac), 2.08(s, 3H, Ac), 2.06(s, 3H, 18-CH_3), 1.91—1.86(m, 2H), 1.78—1.75(m, 1H, 6-H), 1.68(s, 3H, 16-CH_3), 1.18—1.58(m, 1H), 1.16(s, 3H, 17-CH_3), 0.90(s, 3H, 19-CH_3).

19: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 16.0 Hz, 1H, COC*H* = CHPh), 7.59—7.48 (m, 2H, Ph-H), 7.44—7.34(m, 3H, Ph-H), 6.43 (d, J = 16.0 Hz, 1H, COCH = C*H*Ph), 6.04(d, J = 10.3 Hz, 1H, 10-H), 5.79(d, J = 10.3 Hz, 1H, 9-H), 5.63(dd, J = 4.9, 1.9 Hz, 1H, 2-H), 4.66 (d, J = 12.0 Hz, 1H, 20-H), 4.18(d, J = 12.0 Hz, 1H, 20-H), 3.89(t, J = 2.6Hz, 1H, 5-H), 3.30(br. s, 1H, 5-OH), 3.17(d, J = 19.7 Hz, 1H, 14-H), 3.12(d, J = 4.9 Hz, 1H, 3-H), 2.73(dd, J = 19.7, 6.8 Hz, 1H, 14-H), 2.23(s, 3H, Ac), 2.20(s, 3H, Ac), 2.15(dd, J = 6.8, 1.9 Hz, 1H, 1-H), 2.09(s, 3H, Ac), 2.03(s, 3H, 18-CH_3), 1.91—1.82(m, 1H), 1.77(s, 3H, 16-CH_3), 1.74—1.57(m, 3H), 1.15(s, 3H, 17-CH_3), 0.89(s, 3H, 19-CH_3).

Preparation of compound **20** A solution of a mixture of **17** and **18** (260 mg, 0.4058 mmol) in methanol (26 mL) was treated with 1N aqueous K_2CO_3 (4.06 mL, 2.029 mmol) at 0℃ for 4.5 h. The reaction was quenched with 5% aqueous HCl (pH 7). The resulting solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (60 mL). The organic layer was washed with brine, dried (Na_2SO_4), concentrated and the residue was purified by chromatography (silica gel, hexane/acetone 1:1) to give product

20 (158 mg, 83%).

Preparation of compound **21** A solution of **20** (130 mg, 0.2775 mmol) in pyridine (10 mL) was treated with acetic anhydride (524 mL, 5.549 mmol) at 25℃ for 48 h. The reaction was quenched with ice (10 g). The resulting solution was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), concentrated and the residue was purified by chromatography (silica gel, hexane/acetone 4:1) to give **21** (80 mg, 52%) as a white solid, mp 211—213℃. ^1H NMR (500 MHz, $CDCl_3$): δ 6.03(d, J = 10.3 Hz, 1H, 10-H), 5.78(d, J = 10.3 Hz, 1H, 9-H), 5.60(dd, J = 5.1, 2.1 Hz, 1H, 2-H), 4.50(d, J = 12.0 Hz, 1H, 20-H), 4.06 (d, J = 12.0 Hz, 1H, 20-H), 3.81(br. s, 1H, 5-H), 3.19(s, 1H, 4-OH), 3.13(d, J = 19.7 Hz, 1H, 14-H), 3.09(d, J = 5.0 Hz, 1H, 3-H), 2.73 (dd, J = 19.8, 6.9 Hz, 1H, 14-H), 2.54(br. s, 1H, 5-OH), 2.21(s, 3H, Ac), 2.19(s, 3H, Ac), 2.14(dd, J = 6.7, 1.8 Hz, 1H, 1-H), 2.09(s, 3H, Ac), 2.08(s, 3H, Ac), 2.03(s, 3H, 18-CH_3), 1.87—1.81(m, 1H, 7-H), 1.79—1.76(m, 1H, 6-H), 1.76(s, 3H, 16-CH_3), 1.69—1.62(m, 1H, 7-Hor 6-H), 1.60—1.51(m, 1H, 6-H or 7-H), 1.14 (s, 3H, 17-CH_3), 0.85(s, 3H, 19-CH_3). FAB MS m/z: 591 ($M + K^+$). Anal. $C_{28}H_{40}O_{11}$. Calcd.: C, 60.86; H, 7.30. Found: C, 60.58; H, 7.33.

Preparation of compound **22** To a stirred solution of **21** (264 mg, 0.478 mmol) in pyridine (10 mL) at 25℃ was added methanesulfonyl chloride slowly and stirring was continued overnight. Then the reaction mixture was poured into ice-water (40 mL), extracted with ethyl acetate (2 × 40mL). The organic extracts were washed with dilute HCl, aqueous $NaHCO_3$, brine, dride over Na_2SO_4 and concentrated to give crude product, which was purified by column chromatography (hexane/acetone 2:1) to yield **22** (249 mg, 83%), mp 230℃ (dec.). ^1H NMR (500 MHz, $CDCl_3$): δ 6.02(d, J = 10.4Hz, 1H, 10-H), 5.79(d, J = 10.4 Hz, 1H, 9-H), 5.62(dd, J = 4.8, 1.9 Hz, 1H, 2-H), 4.97(dd, J = 3.2, 2.1 Hz, 1H, 5-H), 4.73 (d, J = 12.3 Hz, 1H, 20-H), 3.98(d, J = 12.3 Hz, 1H, 20-H), 3.19(s, 1H, 4-OH), 3.08(d, J = 19.8 Hz, 1H, 14-H), 3.00(s, 3H, CH_3SO_2-), 2.97 (d, J = 4.7Hz, 1H, 3-H), 2.75(dd, J = 19.8, 6.8 Hz, 1H, 14-H), 2.25(s, 3H, Ac), 2.17(s, 3H, Ac), 2.15(dd, J = 6.7, 1.8 Hz, 1H, 1-H), 2.12 (s, 3H, Ac), 2.09(s, 3H, Ac), 2.04(s, 3H, 18-CH_3), 2.04—2.00(m, 1H, 6-H), 1.88—1.85(m, 1H, 6-H), 1.76(s, 3H, 16-CH_3), 1.79—1.70(m, 2H, 7-H), 1.16(s, 3H, 17-CH_3), 0.88(s, 1H, 19-CH_3). FAB MS m/z: 631 ($M + H^+$). Anal. $C_{29}H_{42}O_{13}S$. Calcd. C, 55.23; H, 6.71; S, 5.08. Found: C, 55.41; H, 6.81; S, 5.28.

Preparation of compound **23** To a solution of **19** (60 mg, 0.094 mmol) in pyridine (1.2 mL) was added methanesulfonyl chloride (33 mL, 0.421 mmol) and the reaction mixture was stirred at 25℃ for 24 h, then quenched with ice (5 g), extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$, dried over Na_2SO_4, concentrated and purified by preparative TLC (silica gel, petroleum ether/acetone 2:1) to yield **23** (48 mg, 72%). R_f = 0.5.

Preparation of compound **24** *Method A*. To a solution of **22** (249 mg, 0.395 mmol) in a mixed solvent (methanol 30 mL, CH_2Cl_2 5 mL) at 0℃ was added K_2CO_3 (109 mg, 0.790 mmol in 1.5 mL of H_2O) dropwise. The reaction mixture was stirred at 0℃ for 30 min, then HCl (1 N, 1.58 mL) was added slowly, diluted with brine (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, concentrated and chromatographed (hexane/acetone 1:1) to give product **24** (182 mg, 85%).

Method B. A solution of **23** (33 mg, 0.046 mmol) in methanol (1.2 mL) was treated with aqueous K_2CO_3 (1 N, 0.138 mL, 0.069 mmol) at −10 to −5℃ for 40 min, then neutralized with 0.5% aqueous HCl. After being concentrated, the residue was taken up with ethyl acetate (20 mL), washed with brine, dried over Na_2SO_4, concentrated and chromatographed (hexane/acetone 2:1) to give **24** (20 mg, 76 %). ^1H NMR (500 MHz, $CDCl_3$): δ 5.98(d, J = 10.4 Hz, 1H, 10-H), 5.72(d, J = 10.4 Hz, 1H, 9-H), 4.86 (t, J = 2.7Hz, 1H, 5-H), 4.46(s, 1H, OH), 4.25 —4.30(m, 2H, 2-H and 20-H), 4.18(d, J = 9.1 Hz, 1H, OH), 3.66(dd, J = 11.0, 5.5 Hz, 1H, 20-H), 3.04(s, 4H, SO_2CH_3 and OH), 2.96(d, J = 20.0 Hz, 1H, 14-H), 2.79(dd, J = 20.0, 6.7 Hz, 1H, 14-H), 2.68(d, J = 4.9 Hz, 1H, 3-H), 2.30 (dd, J = 6.7, 1.8 Hz, 1H, 1-H), 2.22(s, 3H, 18-

CH_3), 2.09(s, 3H, Ac), 2.03(s, 3H, Ac), 2.05—2.00(m, 1H, 6-H), 1.90—1.85(m, 1H, 6-H), 1.75—1.65(m, 2H, 7-H), 1.68(s, 3H, 16-CH_3), 1.18(s, 3H, 17-CH_3), 0.92(s, 3H, 19-CH_3). FAB MS *m/z*: 585 ($M+K^+$).

Preparation of compound **25** A solution of **24** (8 mg, 0.015 mmol) in toluene (0.5 mL) was treated with DBU (3 mL), 0.022 mmol) at 105℃ for 1.5 h, then cooled to 25℃ and diluted with cthyl acetate (10 mL). The resulting solution was washed with 0.5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, concentrated and purified by preparative TLC (silica gel, hexane/acetone 3:2) to give **25** (3 mg, 46%). ^1H NMR (500 MHz, $CDCl_3$): δ 5.92 (d, *J* = 10.4 Hz, 1H, 10-H), 5.82(d, *J* = 10.4 Hz, 1H, 9-H), 4.75(d, *J* = 8.6 Hz, 1H, 20-H), 4.72(dd, *J* = 9.2, 3.1 Hz, 1H, 5-H), 4.38(d, *J* = 8.6 Hz, 1H, 20-H), 4.37—4.30(m, 1H, 2-H), 3.68(s, 1H, OH), 2.81—2.72(m, 2H, 14-H), 2.63(d, *J* = 9.1 Hz, 1H, OH), 2.29—2.22(m, 1H, 1-H), 2.20—2.10(m, 1H, 6-H), 2.12(s, 1H, Ac), 2.13(d, *J* = 5.5 Hz, 1H, 3-H), 2.05(s, 3H, 18-CH_3), 2.04(s, 3H, Ac), 1.95—1.88(m, 1H, 6-H), 1.72(s, 3H, 19-CH_3), 1.35(s, 3H, 17-CH_3), 1.35—1.25(m, 2H, 7-H), 1.20(s, 3H, 16-CH_3). ^{13}CNMR(125MHz, $CDCl_3$): δ200.5, 170.5, 169.5, 150.8, 137.6, 87.4, 81.9, 76.6, 75.3, 73.0, 69.4 50.2, 48.7, 41.7, 38.0, 37.7, 35.0, 28.7, 26.8, 25.0, 20.9, 20.8, 16.6, 13.6. HR FAB MS Calcd. for $C_{24}H_{34}O_8$ ($M+H^+$): 451.2326. Found: 451.2325.

Compound **27** To a stirred solution of **26** (200 mg, 0.3263 mmol) and DMAP (797 mg, 6.526 mmol) in CH_2Cl_2 (8 mL) was added acetic anhydride (1.23 mL, 13.052 mmol). The reaction mixture was stirred at 35℃ for 5 h. The reaction was quenched with ice (2 g). The resulting solution was diluted with CH_2Cl_2 (40 mL), then the organic layer was washed with 5% aqueous HCl, brine, saturated aqueous $NaHCO_3$, brine respectively. The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by chromatography (silica gel, hexane/ Et_2O 2:1) to give **27** (127 mg, 56%) as a white solid, mp 68—71℃. ^1H NMR (500MHz, $CDCl_3$): δ[8.12(d*, *J* = 7.3Hz) + 8.08 (d*, *J* = 7.3 Hz), 2H, Ph-*o*], 7.59(t*, *J* = 7.4 Hz, 1H, Ph-*p*), 7.48(t*, *J* = 7.3 Hz, 2H, Ph-*m*), 6.00(dd, *J* = 12.2, 5.5Hz, 1H, 10-H), 5.77—5.70 (m, 1H, 2-H), 5.02(d, *J* = 9.2 Hz, 1H, 5-H), [4.49(d, *J* = 8.0 Hz,) + 4.46(d, *J* = 7.9 Hz), 1H, 20-H], 4.13—4.08(m, 2H, 20-H and 14-H), [12.14(s) + 5.23(s) + 3.68(d, *J* = 15.4 Hz) + 3.55(d, *J* = 15.6 Hz), 2H, 4-$COCH_2CO$], [2.80 (d, *J* = 6.0 Hz) + 2.75(d, *J* = 5.7 Hz), 1H, 3-H], 2.56—2.48(m, 1H, 9-H), 2.35—2.18(m, 3H, 6-H and 2 × 13-H), 2.08(s, 3H, Ac), 2.06(s, 3H, Ac), 2.03—1.97(m, 1H, 6-H), 1.95—1.89 (m, 4H, 18-CH_3 and 6-H), [1.86(d, *J* = 3.1 Hz) + 1.85(d, *J* = 3.1 Hz), 1H, 1-H], 1.72(s, 3H, 19-CH_3), 1.60—1.58(m, 2H, 9-H and 7-H), [1.40 (s) + 1.37(s), 3H, 17-CH_3], [1.12(s) + 1.10 (s), 3H, 16-CH_3], 0.72(q, *J* = 8.0 Hz, 9H, TES-CH_3), 0.44—0.31(band, 6H, TES-CH_2). FAB MS *m/z*: 735($M+K^+$). Anal. $C_{39}H_{56}O_9Si$. Calcd.: C, 67.21; H, 8.10. Found: C, 67.49; H, 8.36. (*: with fine structure).

Preparation of compound **29** To a solution of **26** (500 mg, 0.8158 mmol) in THF (13.5 mL) was added lithium bis(trimethyl) silylamide (LiHMDS, 979 mL, 0.979 mmol, 1.0 M solution in THF) under N_2 at 0 ℃ for 0.5 h, followed by acetyl chloride (70 μL, 0.979 mmol). The solution was stirred at 0℃ for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (6 mL). The resulting solution was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), concentrated and the residue was purified by chromatography (silica gel, hexane/ Et_2O 2:1 to 1:1) to give **29** (270 mg, 50.5%) as a white solid and recovered **26** (170 mg, 34%). **29**: mp 68—70℃. ^1H NMR (500 MHz, $CDCl_3$): δ 8.12(d*, *J* = 6.7 Hz, 2H, Ph-*o*), 7.58(t*, *J* = 6.7 Hz, 1H, Ph-*p*), 7.47(t*, *J* = 8.0 Hz, 2H, Ph-*m*), 6.00 (dd, *J* = 12.2, 4.9 Hz, 1H, 10-H), 5.72(dd, *J* = 6.1, 3.1 Hz, 1H, 2-H), 4.96(d, *J* = 8.5 Hz, 1H, 5-H), 4.47(d, *J* = 7.7 Hz, 1H, 20-H), 4.15(dd, *J* = 8.6, 3.7 Hz, 1H, 14-H), 4.09(d, *J* = 7.7 Hz, 1H, 20-H), 2.74(d, *J* = 5.5 Hz, 1H, 3-H), 2.51 (dd, *J* = 14.7, 12.8 Hz, 1H, 9-H), 2.39(dd, *J* = 18.9, 3.7 Hz, 1H, 13-H), 2.34(dd, *J* = 18.9, 8.5 Hz, 1H, 13-H), 2.28(s, 3H, 4-Ac), 2.24—2.16 (m, 2H, 2 × 6-H), 2.06(s, 3H, 10-Ac), 2.04—1.96(m, 1H, 7-H), 1.93(s, 3H, 18-CH_3), 1.92—

1.87(m, 1H, 7-H), 1.86(d, J = 3.1 Hz, 1H, 1-H), 1.72(s, 3H, 19-CH_3), 1.56(dd, J = 14.7, 4.9 Hz, 1H, 9-H), 1.36(s, 3H, 17-CH_3), 1.12(s, 3H, 16-CH_3), 0.72(t, J = 8.0Hz, 9H, TES-CH_3), 0.45—0.31(m, 6H, TES-CH_2). FAB MS m/z: 693($M+K^+$). Anal. $C_{37}H_{54}O_8Si$. Calcd: C, 67.86; H, 8.31. Found: C, 67.76; H, 8.43. (*: with fine structure).

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