Natural Products

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Synthetic Study Towards Azadirachtin: An Efficient and Stereoselective Construction of the AB Rings with Full Functionality**

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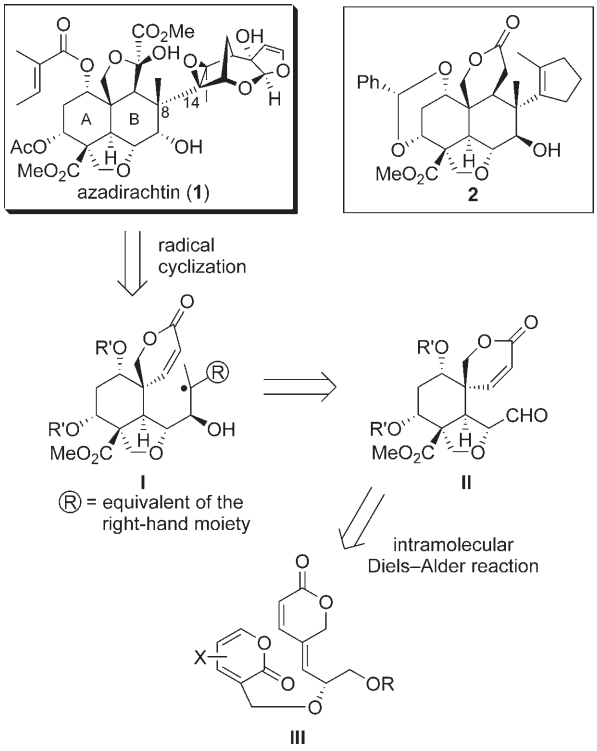
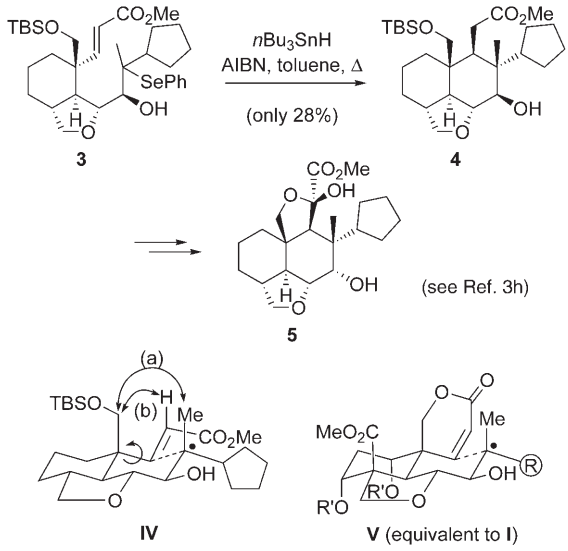
Azadirachtin (**1**) is a C-*seco*-limonoid isolated from the neem tree *Azadirachta indica* A. Juss (Meliaceae)[1] and possesses potent antifeedant activity and growth inhibitory properties against insects.[2] Its complicated structure and biological properties fascinate synthetic chemists, and although many synthetic efforts have been made, the total synthesis of azadirachtin has not yet been reported.[3] Herein, we report an efficient synthesis of a model compound **2** (Scheme 1), in which the AB rings contain the full functionality of the natural product, including a simplified version of the ring attached at C8.

As shown in Scheme 1, our plan was to introduce the simplified ring Ⓡ to compound **II** prior to the formation of the B ring by using a radical cyclization of **I**. A coupling of the aldehyde **II** with a right-hand segment was expected to be more straightforward than the strategies reported by the research groups of Ley,[3a,b] Murai,[3c] and Nicolaou,[3d–g] in which intramolecular reactions were used to couple two fragments between the sterically crowded C8- and C14-positions. We previously reported the results of a simpler model study for the key radical cyclization reaction (**3**→**4**, Scheme 2), following which compound **4** was successfully converted into **5** after several steps that included an inversion of the secondary alcohol and an oxidation of the position α to the ester carbonyl.[3h] However, the yield of the radical cyclization reaction was unsatisfactory (28%), probably because of steric repulsion of the CH_2OTBS group with the methyl group and the olefinic proton (a and b in the transition-state structure **IV**, respectively; Scheme 2). We thought the latter effect (b) made the angle of the sp^2 plane unsuitable for undergoing attack by the radical, and we thus decided to constrain the geometry of the double bond in a



Scheme 1. Structures of azadirachtin (**1**), model compound **2**, and a retrosynthetic analysis.



Scheme 2. Steric effects observed in our previous study on the radical cyclization. AIBN = 2,2′-azobisisobutyronitrile, TBS = *tert*-butyldimethylsilyl.

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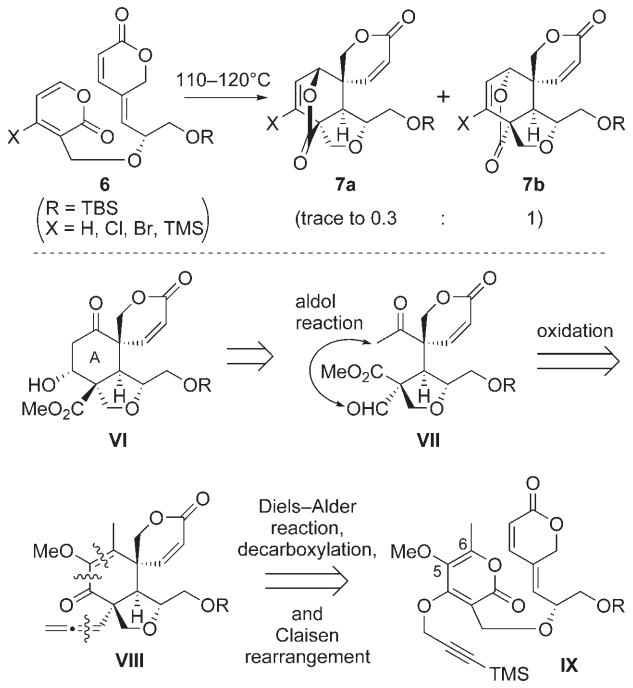
lactone **V**. The most straightforward access to the spiro lactone **II** would be a unique intramolecular Diels–Alder (IMDA) reaction between an α-pyrone and a double bond between the γ and δ positions of a dienolide such as **III**.

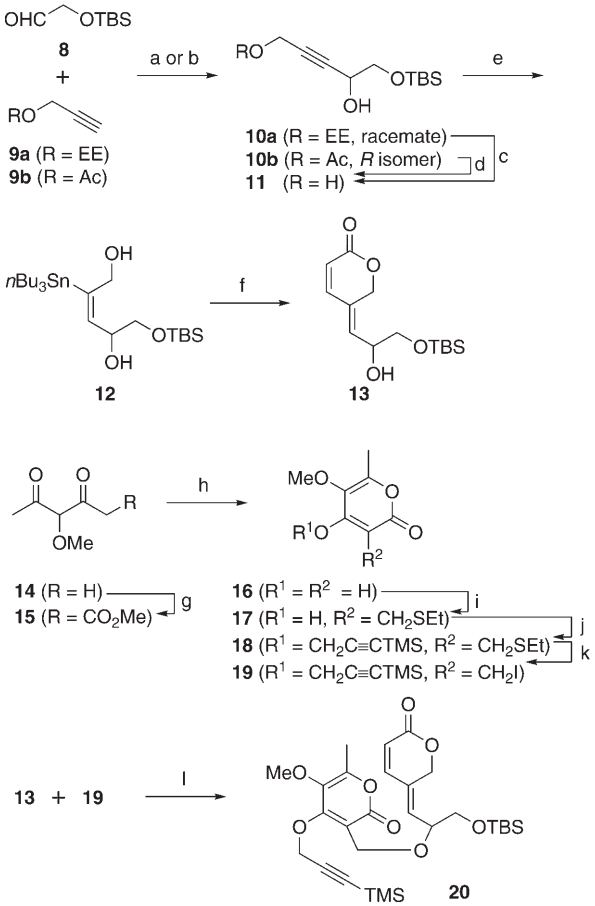
Initially IMDA reactions (**6** to **7**, Scheme 3) on substrates with diverse substituents on the pyrone ring were investigated and were found to proceed smoothly with excellent yields in



Scheme 3. Undesired stereoselectivity observed from the Diels–Alder reaction and the revised synthetic approach. TMS = trimethylsilyl.

all cases. However, to our disappointment, the desired isomers **7a** were obtained only as the minor product from the reactions. During these investigations we observed that an IMDA adduct of a pyrone with a methyl group at C6 readily decarboxylated, and this result fortunately enabled us to use both stereoisomers. Thus, by decarboxylation of the two diastereomeric IMDA adducts of **IX**, the quaternary chiral centers at the bridgeheads would be removed to afford the same intermediate, and an equivalent of the lost carbon unit could be introduced again as an allene by a Claisen rearrangement from the less-hindered convex side (Scheme 3). The A ring would be constructed with the desired stereochemistry by oxidative cleavage of a cyclohexenone ring and an allene in **VIII** followed by recyclization of the resulting intermediate **VII** by using an aldol reaction.

On the basis of the strategy described above, we prepared the precursor to the key IMDA reaction as shown in Scheme 4. Aldehyde **8** was treated with the lithium acetylide derived from **9a**, and the ethoxyethyl (EE) group of the product **10a** was removed to afford the racemic diol **11**. Alternatively, optically active **11** could be synthesized from the reaction of **8** with **9b** via (*R*)-**10b** (98% *ee*) by a modification of the asymmetric procedure reported by Carreira and co-workers,[4] and subsequent removal of the



Scheme 4. Preparation of the dienophile, the pyrone, and their coupling. Reagents and conditions: a) *n*BuLi, THF, −78°C, 94% (from **9a** to **10a**); b) $Zn(OTf)_2$, Et_3N, (1*R*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)propan-1-ol, toluene, RT, 64% (**9b**→**10b**); c) PPTS, EtOH, RT, 66%; d) DIBALH, CH_2Cl_2, −78°C, 87%; e) nBu_3SnH, $[Pd(PPh_3)_4]$, THF, 0°C; f) (*Z*)-ICH=$CHCO_2Me$, copper(I) thiophene-2-carboxylate, NMP, 0°C→RT, 50% (2 steps); g) LDA, $ClCO_2Me$, ether, −78→0°C, 82%; h) DBU, C_6H_6, reflux; i) EtSH, $(CH_2O)_n$, $CHCl_3$, reflux, 91% (2 steps); j) TMSC≡CCH_2OTs, K_2CO_3, [18]crown-6, acetone, RT, 40%; k) MeI, C_6H_6, reflux, 87%; l) AgOTf, 4-A MS, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0°C→RT, 88%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBALH = diisobutylaluminum hydride, LDA = lithium diisopropylamide, NMP = *N*-methylpyrrolidone, PPTS = pyridinium toluene-*p*-sulfonate, Tf = trifluoromethanesulfonyl, Ts = toluene-*p*-sulfonyl.

acetyl group. We decided to use racemic **11** for initial investigations into further transformations. Palladium-catalyzed hydrostannation[5] of **11** gave an inseparable mixture of **12** and its regioisomer (ca. 4:1) and subsequent Cu^I-mediated coupling[6] with methyl (*Z*)-3-iodoacrylate directly afforded the desired lactone **13**, the dienophile for the IMDA reaction.

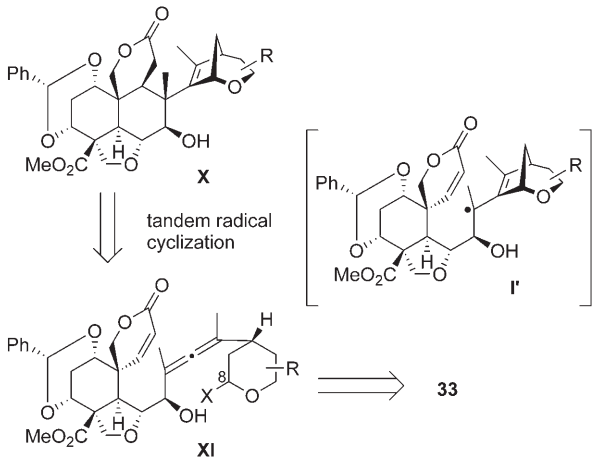
For the preparation of the tetrasubstituted pyrone, 3-methoxy-2,4-pentanedione (**14**)[7] was first methoxycarbonylated and the resulting diketo ester **15** was treated with DBU to form the pyrone ring.[8] Successive ethylthiomethylation, propargyl etherification, and substitution of the ethylthio group with iodide afforded **19**. Coupling of **13** and **19** to give **20** (Table 1) was performed successfully by the well-known glycosylation method.[9]

The next tasks were the IMDA reaction and construction of the A ring as depicted in Scheme 5. The IMDA reaction and subsequent decarboxylation proceeded smoothly at 120 °C in DMF, and **21** was obtained in good yield (Table 1). After liberation of the terminal acetylene, **22** was heated again to effect the Claisen rearrangement, and allene **23** was obtained as a single isomer in quantitative yield. It should be noted that the Claisen rearrangement took place prior to the IMDA reaction when the acetylene of **20** was not protected with a TMS group.

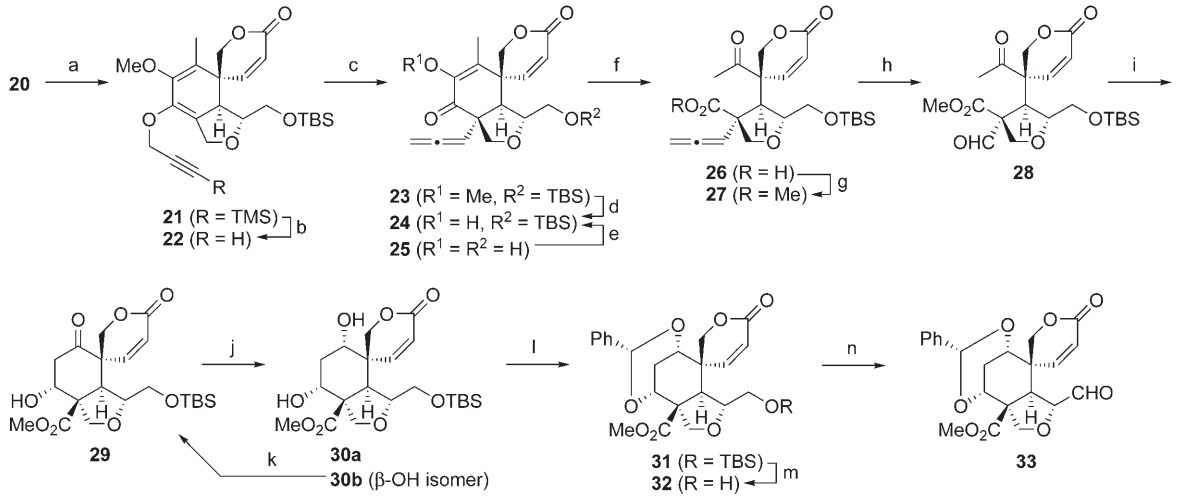
For the cleavage of the cyclohexenone ring, **23** was first transformed into an α-hydroxycyclohexenone **24**. However, treatment of **23** with BBr_3 afforded a significant amount of the diol **25** (67%) along with **24** (24%). Therefore, the primary alcohol of **25** was protected again with a TBS group (87%), and **24** was thus obtained in 82% combined yield. Compound **24** was subjected to an oxidative ring-opening reaction with singlet oxygen,[10] which proceeded quite smoothly and **27** was obtained in excellent yield after esterification of the keto acid **26** with a methyl group. Regioselective ozonolysis of **27** gave the aldehyde **28**; interestingly, the unsaturated lactone was relatively unreactive and remained intact even when an excess of ozone was used. An aldol reaction of **28** under the conditions reported by Mukaiyama et al.[11] afforded a β-hydroxy ketone **29** as a single isomer. The presence of molecular sieves (MS) was essential for the reproducibility of this reaction, and in the absence of 4-Å MS, complete dehydration of the product was often observed. Other basic or Lewis acidic conditions (LDA, LiHMDS, KHMDS, TBSOTf/diisopropylethylamine,[12] nBu_2BOTf/Et_3N,[13] Cy_2BCl/Et_3N,[14] and $TiCl_4/Et_3N$;[15] HMDS = hexamethyldisilazanide, Cy = cyclohexyl) caused only the decomposition of **28**.

The subsequent stereoselective reduction of the ketone proved problematic and, among the several reducing agents examined, only the borane–*tert*-butylamine complex was suitable for the reduction of **29** to provide the desired α isomer **30a** in a moderate yield (43%) along with the undesired stereoisomer **30b** (35%, Scheme 5). Fortunately, **30b** could be recycled back to **29** by using a regioselective monooxidation with Dess–Martin periodinane (DMP). After protecting the *cis*-diol as a benzylidene acetal, the TBS group in **31** was removed to liberate the primary alcohol, which was then oxidized to the aldehyde **33**. This completed the synthesis of the left-hand segment, ready to be coupled with the right-hand moiety.

The next task in the total synthesis of azadirachtin was introduction of the right-hand moiety and formation of the B ring to finish construction of the complete carbon skeleton of the target molecule. We thought that allene **XI** would be an ideal precursor to the intermediate allylic radical **I′** whereby a bridge may be formed between the radical generated at the C8-position and the central carbon atom of the allene (Scheme 6). We therefore examined the possibility of this

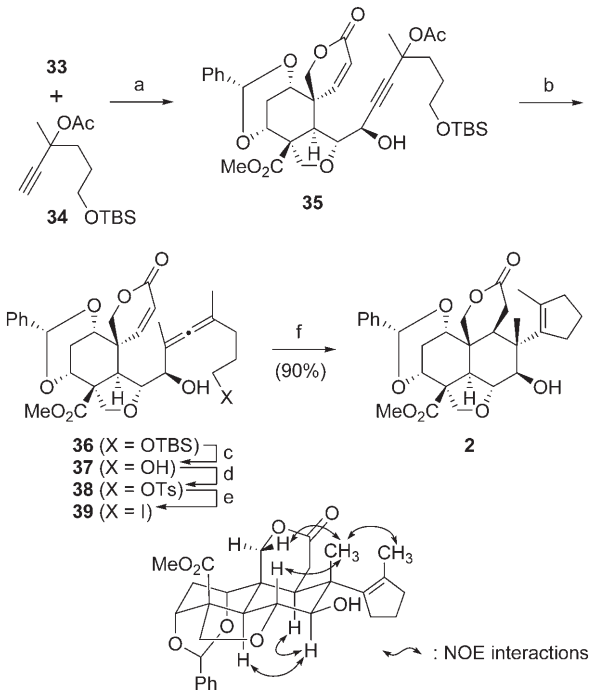


Scheme 6. Tandem radical approach for the construction of the bridged system and the B ring.



Scheme 5. Construction of the A ring. Reagents and conditions: a) DMF, 120 °C, 66%; b) K_2CO_3, MeOH, RT; c) toluene, reflux, quant. (2 steps); d) BBr_3, CH_2Cl_2, 0 °C, 24% (**24**) and 67% (**25**); e) TBSCl, imidazole DMF, RT, 87%; f) O_2, *hν*, methylene blue, MeOH, 0 °C; g) CH_2N_2, EtOAc, 0 °C, 90% (2 steps); h) O_3, CH_2Cl_2, then Me_2S, −78 °C; i) $Sn(OTf)_2$, 4-Å MS, Et_3N, CH_2Cl_2, RT, 74% (2 steps); j) $tBuNH_2{\cdot}BH_3$, CH_2Cl_2, RT, 43% (**30a**) and 35% (**30b**); k) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 74%; l) $PhCH(OMe)_2$, PPTS, C_6H_6, reflux, 87%; m) TBAF, THF, 0 °C→RT, 95%; n) DMP, $NaHCO_3$, CH_2Cl_2, RT. DMF = *N*,*N*-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride.

tandem cyclization approach by using a simplified right-hand segment **34** as shown in Scheme 7.



Scheme 7. Introduction of a simplified right-hand moiety and formation of the B ring. Reagents and conditions: a) LiHMDS, THF, −78 °C, 23% (2 steps from **32**); b) MeMgBr, CuI, LiBr, THF, 0 °C, 78%; c) TBAF, THF, 0 °C→RT, 97%; d) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→RT, 90%; e) NaI, $NaHCO_3$, DMF, RT, 94%; f) $n$$Bu_3SnH$, AIBN, toluene, reflux, 90%. DMAP = 4-dimethylaminopyridine.

Reaction of **33** with the lithiated compound derived from **34** afforded mainly the chelation-controlled product **35** along with a small amount of the α isomer (7%). An S_N2' reaction of the propargyl acetate with a methyl copper reagent afforded the allene **36** as an inseparable 1:1 diastereomeric mixture, which was then converted into the iodide **39** over three steps via the alcohol **37** and the tosylate **38**.

Finally, **39** was subjected to the key tandem radical cyclization reaction ($n$$Bu_3SnH$, AIBN, 110 °C) and, to our delight, the reaction proceeded very smoothly and the desired product **2** was obtained in excellent yield (90%) as a single isomer (Table 1). This result clearly indicates that the constrained conformation of the radical acceptor as an unsaturated lactone was highly effective, as we initially proposed. The stereochemistry of **2** was established by NOE experiments as depicted in Scheme 7.

In conclusion, we have succeeded in the synthesis of an advanced model compound **2** with the complete functionality in the correct position on its decalin ring by employing a Diels–Alder reaction, decarboxylation, Claisen rearrangement, and tandem radical cyclization as key steps. Our approach (23 steps) is significantly shorter than the construction of similar frameworks that have been reported. Preparation of optically active **33** and the right-hand segment for the completion of the total synthesis is now in progress and will be reported in due course.

Table 1: Selected physical properties for compounds **20**, **23**, and **2**.

20: R_f = 0.26 (silica gel, EtOAc/hexanes 1:2); IR (film): $\tilde{\nu}_{max}$ = 2955, 2857, 1730, 1650, 1565, 1449, 1408, 1354, 1251, 1226, 1096, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.98 (1H, d, J = 9.9 Hz), 5.89 (1H, d, J = 9.9 Hz), 5.77 (1H, br d, J = 7.8 Hz), 5.24 (1H, dd, J = 2.1, 14.7 Hz), 5.07 (1H, dd, J = 2.1, 14.7 Hz), 4.91 (2H, s), 4.44 (1H, d, J = 10.5 Hz), 4.39 (1H, d, J = 10.5 Hz), 4.22 (1H, m), 3.78 (1H, dd, J = 5.4, 9.9 Hz), 3.68 (3H, s), 3.51 (1H, dd, J = 7.2, 9.9 Hz), 2.23 (3H, s), 0.84 (9H, s), 0.13 (9H, s), 0.01 (3H, s), 0.00 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 163.4, 163.2, 155.3, 144.5, 135.6, 135.5, 130.9, 118.2, 110.4, 98.5, 94.8, 76.3, 66.9, 65.0, 61.9, 61.8, 61.5, 25.8, 18.3, 14.6, −0.5, −5.4, −5.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{43}O_8Si_2$ $[M+H]^+$: 563.2496, found 563.2448.

23: R_f = 0.30 (silica gel, EtOAc/hexanes 1:2); IR (film): $\tilde{\nu}_{max}$ = 2929, 2855, 1955, 1738, 1676, 1621, 1471, 1379, 1253, 1123, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.76 (1H, d, J = 9.9 Hz), 5.99 (1H, d, J = 9.9 Hz), 5.40 (1H, t, J = 6.6 Hz), 4.87 (2H, d, J = 6.6 Hz), 4.53 (1H, d, J = 11.7 Hz), 4.32 (1H, d, J = 8.1 Hz), 4.31 (1H, d, J = 11.7 Hz), 4.06 (1H, m), 3.79 (1H, dd, J = 3.3, 10.8 Hz), 3.64 (3H, s), 3.62–3.69 (2H, m), 2.88 (1H, d, J = 6.3 Hz), 1.95 (3H, s), 0.88 (9H, s), 0.07 (3H, s), 0.06 ppm (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.6, 192.8, 162.0, 151.7, 150.5, 140.2, 119.8, 90.2, 82.0, 80.6, 79.7, 71.7, 65.2, 59.9, 57.3, 48.2, 40.8, 25.9, 18.3, 13.0, −5.4, −5.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{35}O_6Si$ $[M+H]^+$: 447.2203, found 447.2213.

2: R_f = 0.18 (silica gel, EtOAc/hexanes 1:1); IR (film): $\tilde{\nu}_{max}$ = 3418, 2928, 1731, 1645, 1455, 1417, 1293, 1225, 1197, 1119, 1071, 981 cm^{-1}; ^1H NMR (300 MHz, $C_6D_5CD_3$ at 80 °C): δ = 7.34–7.42 (2H, m), 7.10–7.20 (3H, m), 5.84 (1H, s), 4.77 (1H, d, J = 13.5 Hz), 4.57 (1H, d, J = 5.1 Hz), 4.35 (1H, dd, J = 8.4, 12.3 Hz), 4.00 (1H, d, J = 8.4 Hz), 3.93 (1H, d, J = 13.5 Hz), 3.91 (1H, d, J = 5.1 Hz), 3.82 (1H, d, J = 8.4 Hz), 3.72 (1H, d, J = 8.4 Hz), 3.25 (3H, s), 2.78 (1H, br d, J = 6.9 Hz), 2.71 (1H, d, J = 12.3 Hz), 2.41 (1H, dd, J = 2.4, 18.0 Hz), 2.35 (1H, dd, J = 6.9, 18.0 Hz), 2.25–2.34 (2H, m), 2.24 (1H, dt, J = 15.9, 5.1 Hz), 2.05–2.18 (2H, m), 1.52 (3H, s), 1.46–1.60 (2H, m), 1.38 (1H, d, J = 15.9 Hz), 1.33 ppm (3H, s); ^{13}C NMR (125 MHz, $C_6D_5CD_3$ at 80 °C): δ = 173.5, 168.5, 138.9, 135.4, 126.7, 93.2, 81.5, 76.7, 72.2, 70.5, 69.8, 69.1, 56.1, 51.6, 50.3, 43.3, 42.7, 40.2, 37.1, 30.3, 28.5, 22.4, 21.8, 17.0, 16.3 ppm (three signals of aromatic carbon atoms overlapped with $C_6D_5CD_3$ and were not observable.); HRMS (ESI-TOF): m/z calcd for $C_{30}H_{37}O_8$ $[M+H]^+$: 525.2488, found 525.2515.

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