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Convergent enantioselective syntheses of two potential C25–C40 subunits of (−)-caylobolide A

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ABSTRACT

The convergent syntheses of two possible diastereomers of the C25–C40 subunit resident in (−)-caylobolide A have been accomplished. The key reaction featured a chemoselective Ru-catalyzed cross-metathesis between a fully elaborated type I and two functionalized type II α,β-unsaturated ketones.

Marine sources continually provide the synthetic community a variety of structurally challenging natural products.[1] One aspect that makes the total synthesis of natural products so challenging is the uncertain configuration of multiple stereogenic centers within a target compound. It is well known that diastereomeric possibilities increase exponentially by a factor of 2^n, where n is equal to the number of chiral centers. Thus, the greater number of undefined stereogenic centers can rapidly complicate a synthetic approach. One such natural product, termed caylobolide A (**1**), was isolated via bioassay-guided purification in 2002 from the marine cyanobacteria *Lyngbya majuscule* collected at Cay Lobos, Bahamas by Molinski and MacMillan.[2] As shown in Scheme 1, caylobolide A contains eight undefined stereocenters, thus 256 diastereomeric structural possibilities. Another interesting feature of **1** is the repeating 1,5-diol motif present along the 36-membered lactone core. In addition to its intriguing macrocyclic structure, caylobolide A has shown cytotoxic properties against the human colon tumor cell line HCT 116 (IC_{50} = 9.9 μM). Based on the limited biological data and very unique and challenging structural features of caylobolide A, we sought to undertake the synthesis of **1**. Herein, we disclose our synthetic approach to the C25–C40 subunit of **1**.

The retrosynthetic strategy of caylobolide centered on a highly convergent approach is highlighted in Scheme 1. Thus, we envisaged esterification at C35 (either standard or macrocyclic) and olefin metathesis (either cross or ring-closing) process at C23–C24 to forge the 36-membered ring of **1**. We initially decided to focus on constructing the C25–C40 segment of **1** due to the defined stereocenters (relative configuration via the Kishi universal NMR database and absolute configuration by Mosher analysis) at C25, C27, C29, and C33.[3,4]

With this idea in mind, the two potential C25–C40 segments **2** and **3** would be synthesized via a cross-metathesis of homoallylic alcohol **4** and the two α,β-unsaturated ketones **5** and **6**. We arbitrarily chose the *S*-configuration at C36 for compounds **5** and **6** to simply illustrate the synthetic approach to **2** and **3**.

With the initial synthetic plan in hand, our focus was turned to completing the homoallylic diol **4**. As shown in Scheme 2, treatment of the known TBS protected aldehyde **7**[5] with (+)-Ipc_2Ballyl under the standard reaction conditions as pioneered by Brown furnished the requisite homoallylic alcohol.[6] An ensuing protection of the free hydroxyl group with BnBr, NaH, and Bu_4NI afforded benzyl ether **8** in 69% yield over two steps from **7**. Oxidative cleavage with O_3 and PPh_3 mediated reductive quench of the olefin moiety resident in **8** was readily accomplished and provided the aldehyde **9** in 60% yield. With the required aldehyde in hand, we envisioned a chelation-controlled allylation with an appropriate stannane utilizing the benzyl directing group and $TiCl_4$.[7] Much to our delight, treatment of **9** with $TiCl_4$ and $Bu_3Snallyl$ at −78 °C furnished the desired *anti*-homoallylic alcohol with excellent diastereoselectivity (~12:1 dr) as deduced by ^1H NMR.

An ensuing protection of the free hydroxyl moiety as a TBS ether was readily accomplished under standard reaction conditions (TBSCl and imidazole) to afford the protected diol **4** in 75% yield over two steps from **9**.[8]

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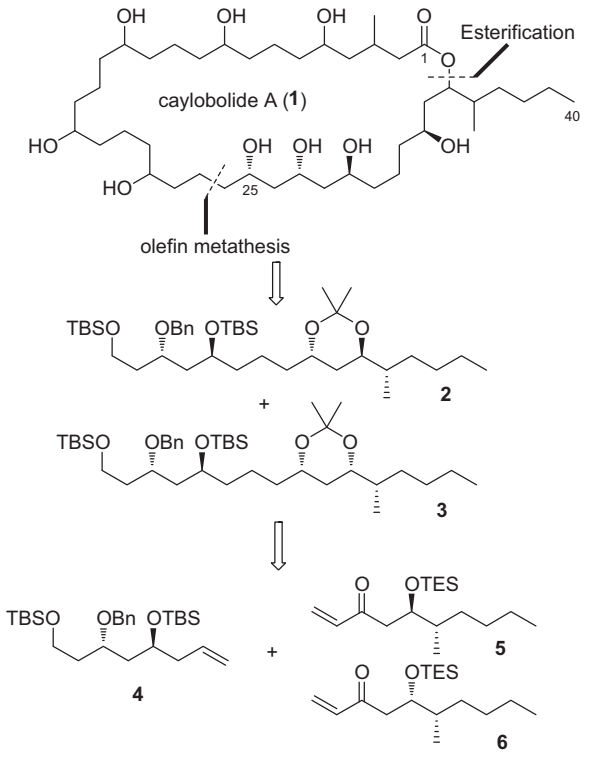
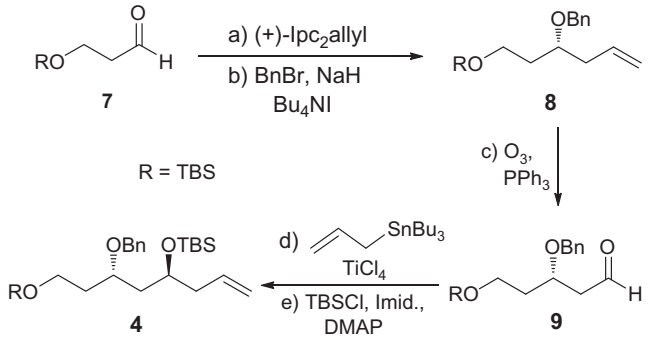
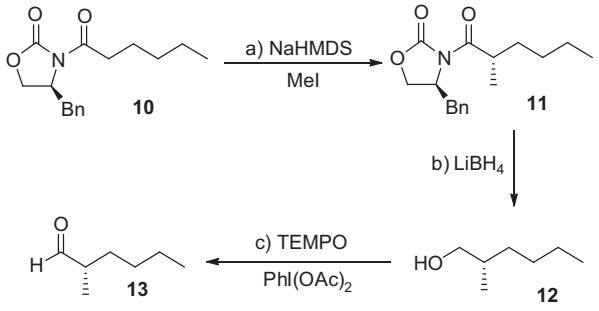


Scheme 1. Retrosynthetic analysis of caylobolide (**1**).



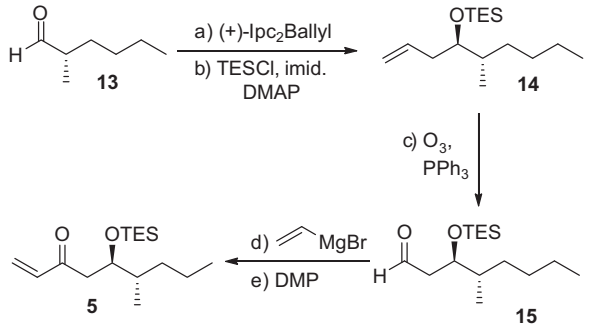
Scheme 2. Synthesis of intermediate **4**. Reagents and conditions: (a) (+)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv) Et$_2$O, 0 °C to −78 °C to rt, 6 h, 83%; (b) BnBr (1.1 equiv), NaH (2.0 equiv), Bu$_4$NI (0.1 equiv), DMF, rt, 24 h, 83%; (c) CH_2Cl_2, −78 °C, then PPH_3 (4.0 equiv), rt, 6 h, 60%; (d) allylSnBu$_3$ (2.0 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 8 h, 81%; (e) TBSCl (2.0 equiv), imidazole (4.0 equiv), DMAP (0.2 equiv), DMF, rt, 24 h, 92%.



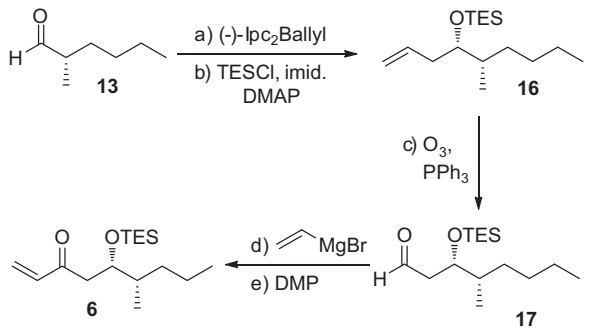
Scheme 3. Synthesis of intermediate **13**. Reagents and conditions: (a) NaHMDS (1.2 equiv), MeI (2.5 equiv), THF, −78 to −20 °C, 2 h, 81%; (b) LiBH$_4$ (3.0 equiv), MeOH (3.0 equiv), Et$_2$O, rt, 6 h, 93%; (c) TEMPO (0.15 equiv), PhI(OAc)$_2$ (1.1 equiv), CH_2Cl_2, rt, 20 h, 82%.

Our outline to the C25–C40 segment of **1** required the synthesis of chiral aldehyde **13** as delineated in Scheme 3. Hence, an asymmetric alkylation of the known chiral oxazolidinone **10** with NaHMDS and MeI provided **11** in 81% yield with excellent diastereoselectivity (>15:1 dr).[9] Subsequent reduction of the oxazolidinone moiety with LiBH$_4$ readily afforded the chiral primary alcohol **12** in 93% yield. Final oxidation of the hydroxyl group of **12** with TEMPO and PhI(OAc)$_2$ furnished the desired aldehyde **13** in 82% yield and set the stage for building the subunits **5** and **6**.[10]

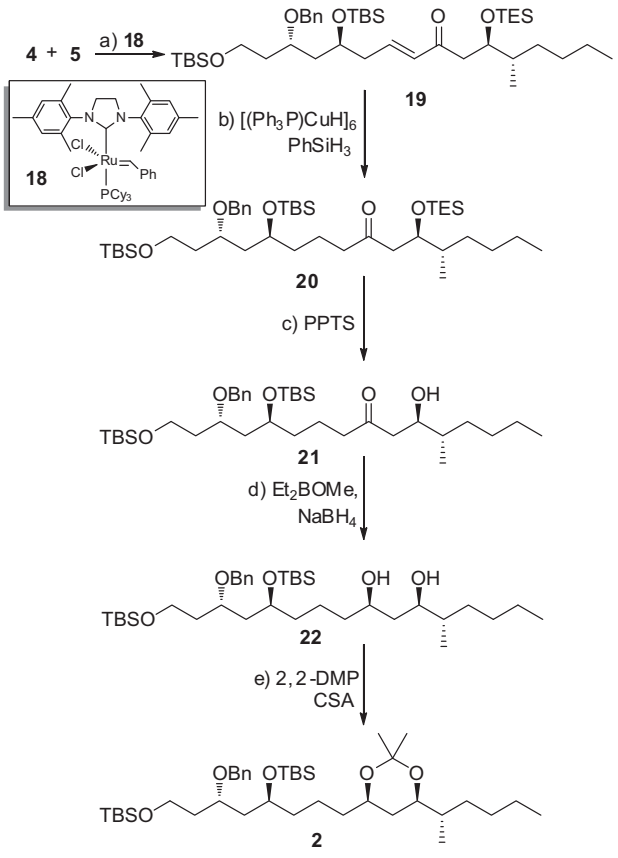
With the chiral aldehyde **13** readily in hand and in multi-gram quantities, we next focused our effort on the completion of the cross-metathesis precursor ketones **5** and **6** as delineated in Schemes 4 and 5. Thus, treatment of the chiral aldehyde **13** with (+)-Ipc$_2$Ballyl provided the corresponding homoallylic alcohol with a respectable 66% yield and dr of ~10:1. Ensuing protection of the free hydroxyl group with TESCl, DMAP, and imidazole furnished the triethylsilyl ether **14** in 73% yield. Ozonolysis of the terminal olefin followed by the addition of PPh_3 resulted in the formation of the requisite aldehyde **15** in 63% yield. In order to complete the cross-metathesis coupling type II olefin **5**, a vinyl addition and subsequent oxidation to furnish the α,β-unsaturated ketone **5** were required. Thus, the addition of vinyl Grignard reagent to **15** provided the allylic alcohol as an extraneous mixture of diastereomers and ensuing oxidation of the hydroxyl moiety with Dess–Martin periodinane (DMP) afforded ketone **5** in 38% yield over two steps from **15**.[11] Access to ketone **6** followed a very similar synthetic pathway, but differed only in utilizing the (−)-Ipc$_2$Ballyl reagent as shown in Scheme 5. All of the other steps (b–e) were



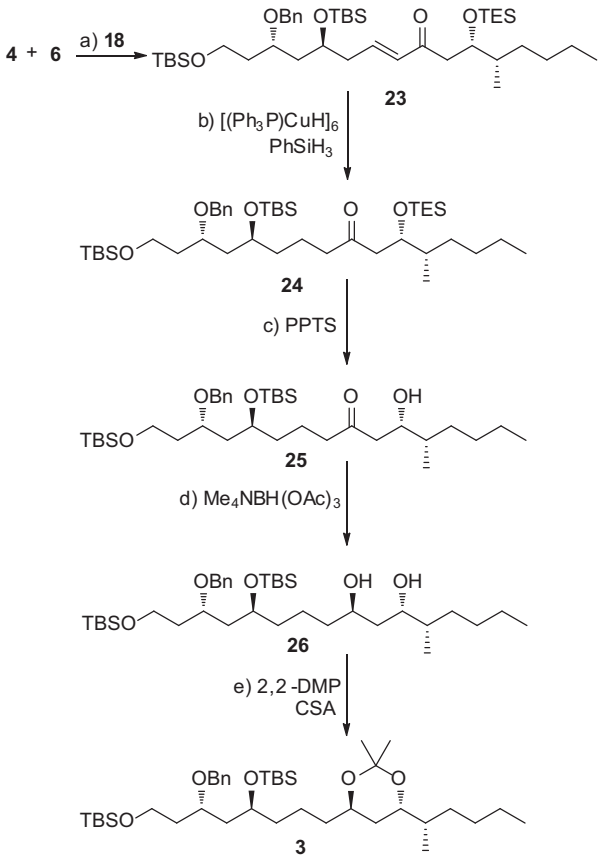
Scheme 4. Synthesis of intermediate **5**. Reagents and conditions: (a) (+)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv), Et$_2$O, −78 °C to rt, 3 h 66%; (b) TESCl (1.5 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h, 73%; (c) CH_2Cl_2 −78 °C, 1 h, then PPh_3 (4.0 equiv), rt, 6 h, 63%; (d) vinylMgBr, (2.0 equiv), Et$_2$O, −78 °C, 4 h, 60%; (e) DMP (2.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, rt, 15 h, 63%.



Scheme 5. Synthesis of intermediate **6**. Reagents and conditions: (a) (−)-Ipc$_2$BOMe (1.6 equiv), allylMgBr (1.5 equiv), Et$_2$O, −78 °C to rt, 3 h 86%; (b) TESCl (1.5 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 12 h, 75%; (c) CH_2Cl_2, −78 °C, 1 h, then PPh_3 (4.0 equiv), rt, 6 h, 60%; (d) vinylMgBr, (2.0 equiv), Et$_2$O, −78 °C, 4 h, 75%; (e) DMP (2.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, rt, 15 h, 70%.



Scheme 6. Synthesis of intermediate **2**. Reagents and conditions: (a) **5** (2.0 equiv), **18** (0.10 equiv), CH_2Cl_2, 40 °C, 24 h, 75%; (b) $[(PhP_3)CuH]_6$ (0.10 equiv) $PhSiH_3$ (1.5 equiv), toluene, rt, 24 h, 70%; (c) PPTS (0.2 equiv), MeOH, CH_2Cl_2 rt, 0.5 h, 80%; (d) Et_2BOMe (1.1 equiv), $NaBH_4$ (1.1 equiv), THF, MeOH, −78 °C, 3 h, 90%; (e) 2,2-DMP (2.0 equiv), CSA (0.10 equiv), CH_2Cl_2, rt, 5 h, 90%.



Scheme 7. Synthesis of intermediate **3**. Reagents and conditions: (a) **6** (2.0 equiv), **18** (0.10 equiv), CH_2Cl_2, 40 °C, 24 h, 77%; (b) $[(PhP_3)CuH]_6$ (0.10 equiv), $PhSiH_3$ (1.5 equiv), toluene, rt, 24 h, 69%; (c) PPTS (0.20 equiv), MeOH, CH_2Cl_2, rt, 0.5 h, 80%; (d) $Me_4NBH(OAc)_3$ (6.0 equiv), MeCN, AcOH, −20 °C, 48 h, 70%; (e) 2,2-DMP (2.0 equiv), CSA (0.10 equiv), CH_2Cl_2, rt, 5 h, 90%.

carried out in an analogous fashion and the isolated yields were quite comparable.

With all the three precursors in hand (type I (**4**) and type II (**5** and **6**) olefins) , we proceeded to converge the aliphatic subunits via a Ru-catalyzed cross-metathesis reaction and complete the C25–C40 segment of **1** as delineated in Schemes 6 and 7.

Inspired by Grubbs' report on selective cross-metathesis, we were hopeful that the treatment of **4** (type I) with an excess of **5** (type II) in the presence of Grubbs' second generation catalyst (**18**) would chemoselectively couple the two subunits.[12,13] In this specific example, the stereochemistry of the corresponding olefin product would be inconsequential, as it would be reduced at a later stage. Hence, the cross-metathesis of **4** with 2.0 equiv of **5** and 10 mol % of **18** readily proceeded to provide **19** in 75% yield with high levels of selectivity for the *E*-isomer. Subsequent conjugate reduction of the α,β-unsaturated carbonyl by means of Stryker's reagent and $PhSiH_3$ afforded the fully saturated compound **20** in 70% yield.[14] A chemoselective desilylation of the TES ether resident in **20** by utilizing PPTS in MeOH furnished β-hydroxy ketone **21** and set the stage for the introduction of the final chiral center in the C25–C40 fragment of **1**.

Thus, a directed *syn*-reduction was readily accomplished upon treatment of ketone **21** with the obligatory reagents (Et_2BOMe and $NaBH_4$) as described by Prasad and afforded diol **22** in 90% with high levels of diastereoselectivity (>20:1 by ^1H NMR).[15] Final protection of the diol moiety resident in **22** utilizing 2,2-dimethoxy propane and a catalytic amount of CSA (10 mol %) furnished acetonide **2** in 90% yield and completed one of the C25–C40 diastereomers of **1**.[16]

Similar to that of ketone **6** in Scheme 5, access to the other C25–C40 diastereomer **3** followed a very similar synthetic pathway to that of **2**.[17] It did, however, differ by utilizing the diastereomeric coupling partner **6** (instead of **5**) and a subsequent $Me_4B(OAc)_3H$ directed *anti*-reduction of the β-hydroxy ketone **25** as shown in Scheme 7. The remaining steps were carried out in a similar manner and the isolated yields were quite comparable.

In conclusion, we have completed the convergent syntheses of two possible diastereomers of the C25–C40 subunit resident in (−)-caylobolide A. One of the key reactions utilized a β-hydroxy directed *anti*-stannane allylation of aldehyde **9** to provide the necessary stereochemistry for the type I olefin coupling partner **4**. In addition, a chemoselective cross-metathesis of **4** with the two diastereomeric α,β-unsaturated ketones **5** and **6** in the presence of catalyst **18** allowed for the completion of the two C25–C40 subunits **2** and **3**. While the remaining stereochemistry of **1** is currently unknown, other natural products suggest that the stereochemistry of the 1,5-diol subunit might be *syn* based on biosynthetic polyketide assembly.[18] However, it is worth noting that the 1,5-diol subunit has been shown to be *anti* in some natural products, that is, marinisporolide A.[18] Studies toward the total synthesis of **1** are ongoing and will be reported in due course.

Acknowledgments

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8. Data for **4**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.4 (m, 4H), 7.3 (m, 1H), 5.8 (m, 1H), 5.1 (m, 2H), 4.6 (d, J = 11.4 Hz, 1H), 4.5 (d, J = 11.4 Hz, 1H), 4.0 (m, 1H), 3.7 (m, 3H), 2.3 (m, 2H), 1.8 (m, 3H), 1.6 (m, 1H), 0.9 (m, 18H), 0.08 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 134.7, 128.2, 127.4, 127.2, 116.8, 73.5, 70.6, 68.9, 59.5, 53.3, 42.5, 42.4, 37.7, 34.1, 25.9, 22.3, 18.2, 18.0, 13.9, −4.1, −4.5, −5.4. IR (CH_2Cl_2): 3072, 3031, 2949, 2927, 2857, 1468, 1431, 1383, 1353, 1253, 1209, 1093, 1004, 934, 912, 837, 804, 774 cm^{-1}. R_f = 0.2, 3% EtOAc in hexane. $[\alpha]_D^{24}$ +3.8° (c 0.034 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{23}H_{41}O_3Si_2$ (M-C_4H_9): 421.2610 found: 421.2594.
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16. Data for **2**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.5 (m, 1H), 7.3 (m, 4H), 4.6 (d, J = 11.4 Hz, 1H), 4.5 (d, J = 11.4 Hz, 1H), 3.9 (m, 1H), 3.7 (m, 4H), 3.5 (m, 1H), 1.7 (m, 3H), 1.5 (s, 6H), 1.4 (m, 5H), 1.3 (m, 7H), 1.2 (m, 5H), 1.0 (m, 2H), 0.89 (m, 18H), 0.83 (d, J = 6.6 Hz, 3H), 0.05 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 129.6, 128.3, 127.5, 98.2, 73.7, 72.7, 70.8, 69.5, 69.0, 59.6, 42.7, 37.8, 37.7, 36.9, 33.1, 32.0, 30.2, 29.1, 25.9, 25.8, 23.0, 20.2, 19.8, 18.2, 18.1, 18.0, 14.3, 14.1, −4.0, −4.3, −5.3. IR (CH_2Cl_2): 3051, 2984, 2852, 2252, 910, 729, 649 cm^{-1}. R_f = 0.84 in 10% EtOAc in hexanes. $[\alpha]_D^{24}$ −0.10 (c 0.084 g/mL, CH_2Cl_2). HRMS (EI) calculated for $C_{35}H_{65}O_5Si_2$ (M-C_4H_9): 621.4375 found: 621.4371
17. Data for **3**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.5 (m, 1H), 7.3 (m, 4H), 4.6 (d, J = 11.4 Hz, 1H), 4.5 (d, J = 11.4 Hz, 1H), 3.7 (m, 4H), 3.5 (m, 2H), 1.7 (m, 3H), 1.4 (m, 8H), 1.3 (s, 6H), 1.2 (m, 5H), 1.1 (m, 3H), 0.97 (m, 2H), 0.88 (m, 21H), 0.04 (m, 12H). ^{13}C NMR (125 MHz, $CDCl^3$) δ 139.0, 129.5, 128.3, 127.5, 100.8, 73.7, 70.8, 70.4, 69.5, 66.8, 59.6, 42.7, 37.7, 37.8, 37.9, 36.7, 36.3, 31.5, 30.8, 29.18, 25.9, 24.7, 24.4, 22.9, 20.8, 18.1, 15.2, 14.0, −4.0, −4.3, −5.3. IR (CH_2Cl_2): 3054, 2986, 2956, 2934, 2857, 2305, 1418, 1267, 893, 733 cm^{-1}. R_f = 0.77 in 10% EtOAc in hexanes. $[\alpha]_D^{24}$ −3.80 (c 0.012 g/mL, CH_2Cl_2) HRMS (EI) calculated for $C_{38}H_{71}O_5Si_2$ (M-CH_3): 663.4832 found: 663.4840.
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