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Synthesis of the racemic tetracyclic core of CP-225,917: use of a strain-assisted Cope rearrangement

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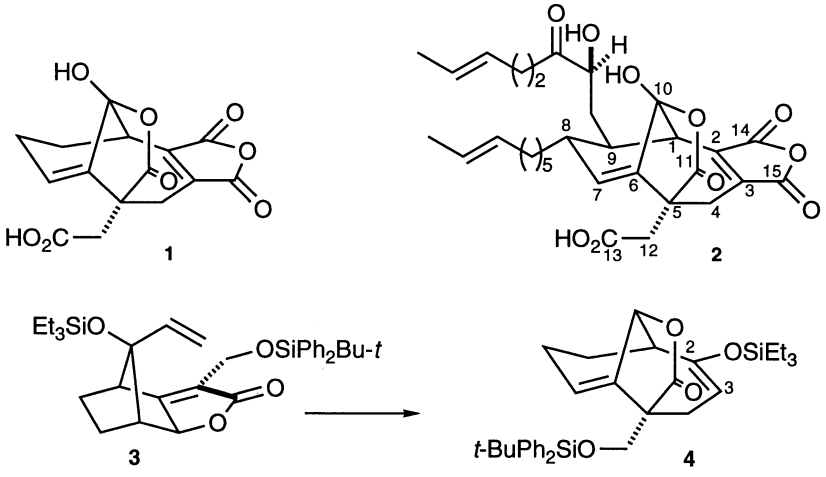
Abstract—Norbornene was converted via diketone **23** into the strained lactone **27**; this was rearranged thermally to lactone **28**, from which point the complete oxygenated core of CP-225,917 is accessible by deprotection and oxidation steps, including a new method for converting a furan system into a hydroxy butenolide. © 2002 Published by Elsevier Science Ltd.

We report the use of a strain-assisted Cope rearrangement in a new route to compound **1**, which is the complete tetracyclic core of CP-225,917 (**2**)[1]—a molecule that has attracted much attention from synthetic chemists,[2–4] because of its unusual structure and potentially important biological properties.[1b]

Previous publications[3] from this laboratory have described methods based on anionic *oxy*-Cope rearrangement, and various forms of *siloxy*-Cope rearrangement to prepare model compounds representing the central part of CP-225,917. These earlier studies[3e] led to the advanced model **1**, which has the full oxygenation pattern of the core. The compound is crystalline and its dimensions were established by X-ray analysis.

Our approaches using the *oxy*- or *siloxy*-Cope rearrangement require that one or both of the anhydride carbons C(14) and C(15)[5] be introduced *after* the rearrangement, and we had found that extensive experimentation was needed to discover a suitable combination of reactions that would introduce these carbons.

Our early experiments involved the rearrangement **3**→**4** (Eq. (1)),[3b] a process that generated the quaternary center and incorporated a silyl enol ether from which we expected to be able to construct the anhydride by attaching carbons C(14) and C(15) at C(2) and C(3), respectively. In the event, accomplishing this task was difficult, and we decided to alter the route by incorporating C(15) *before* generating the [4.3.1]-



(1)

Keywords: Cope rearrangement; strain; anhydride; furan; sodium chlorite; ruthenium dioxide; bridgehead olefin.

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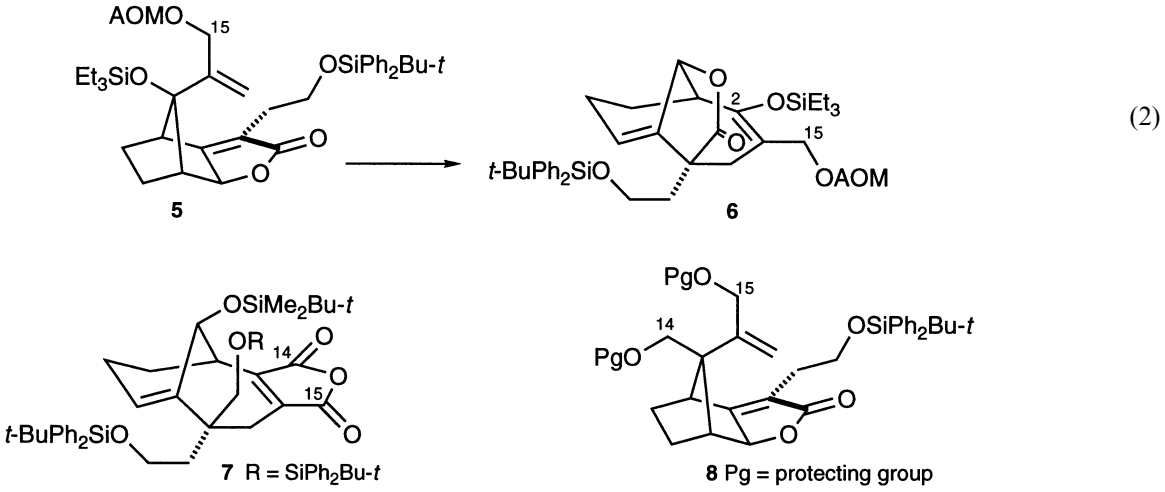
bicyclic carbon skeleton. To this end, we prepared the strained lactone **5**[3d] (AOM = *p*-anisyloxymethyl, *p*-$MeOC_6H_4OCH_2$). This underwent thermal rearrangement to **6** (Eq. (2)), in which C(15) of the final anhydride is already present, so that only C(14) had to be introduced. That was done by treating the C(2) ketone derived from **6** with Tebbe's reagent, and further elaboration then took our model study as far as anhydride **7**.

We found that the route leading to **7** required some modification in order to reach[3e] the more advanced model **1**; in particular, introduction of C(14), which had earlier been achieved with Tebbe's reagent, now, with a slightly different substrate, had to be introduced by a modified[6] Peterson reaction. It was clear that no single method could be relied on for introducing C(14), as seemingly minor structural changes to the substituents on the [4.3.1]-bicyclic framework demanded quite different methods. For this reason, we also examined an alternative route, in which *both* C(14) and C(15) are incorporated early, as in structure **8**, and we report here the successful outcome of such an approach, which now involves a Cope, rather than an *oxy*-Cope, rearrangement, and also relies on a different method for making the anhydride subunit.

Our starting point is the known ester acetal **10**,[7,8] which is easily made on a large (>20 g) scale from norbornene (**9**). Generation of the ester enolate (LDA, THF), followed by condensation with paraformaldehyde, gave alcohol **11** (43%) as the major product, which was then silylated (**11→12**, *t*-$BuPh_2SiCl$, imidazole, DMAP, 86%). The structure of **11** was confirmed by X-ray analysis. Next, treatment with MeLi (Et_2O) afforded ketone **13** (88%). Use of an ester, as opposed to an acid, in this reaction is unusual, but not without precedent.[9] The ketone was converted [$(Me_3Si)_2NK$, THF, $(EtO)_2P(O)Cl$, 85%] into its enol phosphate (**13→14**), and nickel-catalyzed replacement of the $(EtO)_2P(O)O$ group by a methyl group [$Ni(acac)_2$, THF, MeMgBr in Bu_2O, 80%][10] took the route as far as **15**. The ketal was hydrolyzed (THF, 5% HCl, 100%), and the resulting ketone was reduced (DIBAL-H) to a mixture (ca. 1:1) of epimeric alcohols, which were acetylated (Ac_2O, pyridine, DMAP) (**15→16→17→18**). Oxidation (SeO_2, *t*-BuO_2H) of the newly-installed methyl group, followed by reduction of over-oxidized material ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH), and desilylation (Bu_4NF, THF), gave acetates **20** in 68% yield from **16** (**16→17→18→19→20**). The two primary hydroxyls were then protected ($MeOCH_2Cl$, *i*-Pr_2NEt, DMAP, CH_2Cl_2), the acetyl group was removed (DIBAL-H), and the resulting alcohols were oxidized, using the Dess–Martin reagent (**20→21→22**). Ketone **22** was obtained in 45% yield overall from **16**. α-Hydroxylation [$(Me_3Si)_2NK$, THF, MoOPH, ca. 72%] and oxidation (Dess–Martin periodinane, CH_2Cl_2, 56% from **22**) gave diketone **23**. This compound was condensed with the enolate derived from *t*-$BuPh_2SiOCH_2CH_2$–CH_2CO_2Me,[3c] and the resulting crude alcohols were dehydrated ($SOCl_2$, pyridine, room temperature) to the unsaturated keto ester **24**. Reduction ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH) gave hydroxy ester **25** (55% from **23**). Finally, demethylation of the ester (**25→26**, PrSLi, HMPA, 83%) and lactonization (Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 73%) afforded the strained lactone **27**, already carrying suitably functionalized carbons that would ultimately constitute the anhydride carbonyls. Our assignment of the double bond geometry in **24** is based on the subsequent lactonization and the assumption that stereochemical inversion does not occur under the demethylation conditions.

The strained lactone rearranged smoothly in refluxing 1,2-dichlorobenzene to afford tricyclic lactone **28** (Scheme 2), which contains all the carbons needed for elaboration into the desired core model **1**. The Cope rearrangement is slower than the corresponding *siloxy*-Cope process,[3e] but the yield is still high (95%). Global deprotection (**28→29**, MeOH, conc. HCl catalytic, 85%) set the stage for generation of the anhydride. Oxidation with the Dess–Martin reagent converted the allylic diol subunit into a furan and the side chain alcohol into an aldehyde (**29→30**, 85%). Further oxidation, by treatment with $NaClO_2$ under standard conditions for making carboxylic acids (NaH_2PO_4, 2-methyl-2-butene, 12 h), then served the dual purpose



(2)

of generating the side chain carboxyl and transforming the furan into the corresponding hydroxy butenolides (**30**→**31a**,**b**). At that point, TPAP oxidation completed assembly of the anhydride (**31a**,**b**→**32**), the overall yield from furan **30** being 50%. Compound **32** had previously been oxidized[3e] (1N NaOH, 12 h, then RuO_2, 70–80°C, 20 h, $\geq$40%) into the fully oxygenated, crystalline core (**1**) of CP-225,917.

The sequence summarized in Schemes 1 and 2 constitutes a new route to advanced models representing the core structure of CP-225,917, and illustrates the application of strain-assisted Cope rearrangement, as well as a new method[11] for converting a furan into a hydroxy butenolide—a transformation normally accomplished[3e] by photooxygenation.

New compounds, except for **17** and **20**, were characterized spectroscopically, including high resolution mass measurements, but the isomer mixtures **18**, **19**, and **21** were analyzed as epimer mixtures.[12]

Acknowledgements

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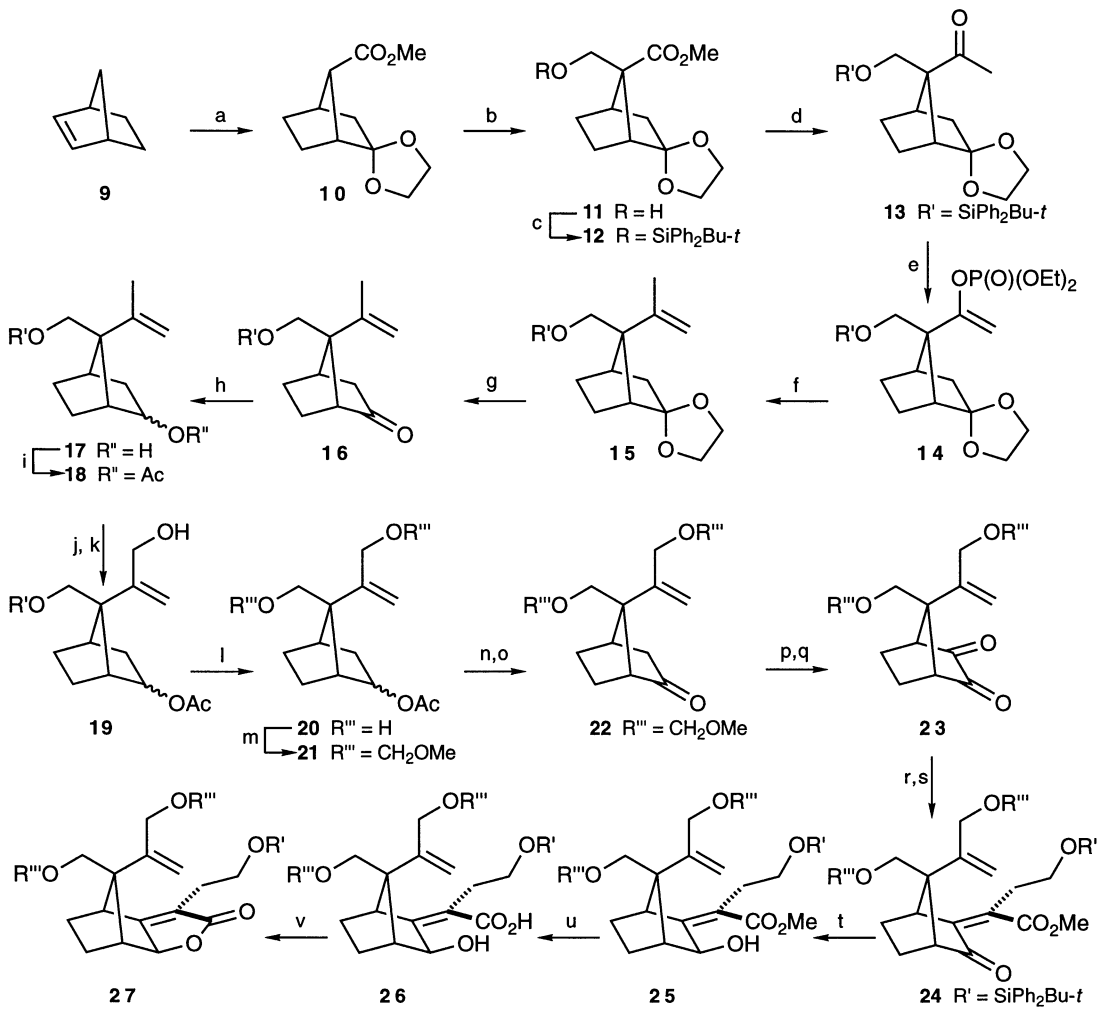
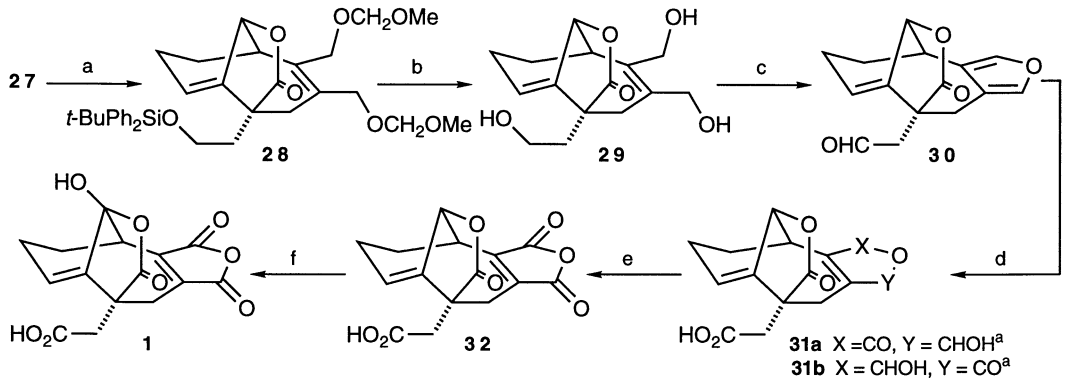


Scheme 1. *Reagents and conditions*: (a) As in Refs. 7, 8a; (b) LDA, THF, −78°C, 45 min, 0°C, 10 min, then −78°C, paraformaldehyde, room temperature, 12 h, 43%; (c) *t*-$BuPh_2SiCl$, imidazole, DMAP, CH_2Cl_2, 30 min, 86%; (d) MeLi, Et_2O, 0°C, 4 h, 88%; (e) $(Me_3Si)_2NK$, THF, $(EtO)_2P(O)Cl$, −78°C, 2 h, 85%; (f) $Ni(acac)_2$, THF, MeMgBr in Bu_2O, 40°C, 12 h, 80%; (g) THF–5% hydrochloric acid, 12 h, 100%; (h) DIBAL-H, CH_2Cl_2, −78°C, 30 min; (i) Ac_2O, pyridine, DMAP, 4 h; (j) SeO_2, *t*-BuO_2H, CH_2Cl_2, 2 days; (k) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, 30 min; (l) Bu_4NF, THF, 5 min, 68% from **16**; (m) MOMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 12 h; (n) DIBAL-H, CH_2Cl_2, −78°C, 20 min, (o) Dess–Martin periodinane, CH_2Cl_2, 10 min, 45% from **16**; (p) $(Me_3Si)_2NK$, THF, −78°C, 1 h, 10 min, 0°C, then −23°C, MoOPH, room temperature, 10 min, ca. 72%; (q) Dess–Martin periodinane, CH_2Cl_2, 15 min, 56% from **22**; (r) LDA, *t*-$BuPh_2SiOCH_2CH_2CH_2CO_2Me$, THF, 1 h, −78°C, then add **23**, 15 min; (s) $SOCl_2$, pyridine, room temperature, 4 h; (t) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, 30 min, 55% from **23**; (u) PrSLi, HMPA, 3 h, 83%; (v) Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, reflux, 18 h; 73%.



Scheme 2. *Reagents and conditions*: [a]Isomer mixture. (a) 1,2-Dichlorobenzene, reflux, 6 h, 95%; (b) MeOH, HCl (catalytic), 62°C, 2 h, 85%; (c) Dess–Martin periodinane, CH_2Cl_2 plus trace DMSO, 12 h, 85%; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 12 h; (e) 4 Å molecular sieves, CH_2Cl_2 plus trace DMSO, TPAP, NMO, 0°C, 3 h, 50% from **30**; (f) as in Ref. 3e [1N NaOH, 12 h, then RuO_2, 70–80°C, 20 h, $\geq$40%].

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11. We found that 5,6,7,8-tetrahydro-4*H*-cyclohepta[*c*]furan was also converted into the corresponding hydroxy butenolide (75%) with the $NaClO_2/NaH_2PO_4$/2-methyl-2-butene system.
12. Characterization data for selected compounds: The symbols s, d, t and q in ^{13}C NMR spectra refer to 0, 1, 2 and 3 attached protons, respectively. **11**: mp 150–152°C; FTIR (CH_2Cl_2/MeOH, cast) 3457, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.35–1.42 (m, 1H), 1.50–2.00 (m, 5H), 2.35–2.42 (m, 3H), 3.70–3.90 (m, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.2 (t), 26.7 (t), 37.9 (d), 42.9 (d), 47.8 (d), 51.8 (q), 63.0 (t), 63.8 (t), 63.9 (s), 64.1 (t), 114.9 (s), 175.1 (s); exact mass m/z calcd for $C_{12}H_{18}O_5$ 242.11542, found 242.11529. **15**: mp 112–114°C; FTIR

(CH_2Cl_2, cast) 3049, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) 1.05 (s, 9H), 1.15–1.60 (m, 3H), 1.70–1.90 (m, 5H), 2.03 (br s, 1H), 2.20–2.30 (m, 1H), 2.40 (br s, 1H), 3.40–4.00 (m, 6H), 4.80 (br s, 1H), 4.95 (br s, 1H), 7.35–7.45 (m, 6H), 7.65–7.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.4 (s), 21.3 (t), 21,71 (q), 26.8 (t), 26.8 (q), 38.6 (d), 42.3 (t), 46.7 (d), 63.1 (t), 63.3 (t), 64.1 (t), 113.1 (s), 116.3 (t), 127.5 (d), 129.3 (d) 133.6 (s), 133.9 (s), 135.6 (d), 135.7 (d), 149.5 (s); exact mass m/z calcd for $C_{29}H_{38}O_3Si$, 462.25903, found 462.25767. **23**: FTIR ($CDCl_3$, cast) 2948, 1775, 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) 1.75–1.83 (m, 2H), 2.00–2.10 (m, 2H), 3.24–3.26 (m, 1H), 3.35 (s, 6H), 3.70 (s, 2H), 4.07 (s, 1H), 4.75 (s, 2H), 4.82 (s, 2H), 5.15 (s, 1H), 5.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.54 (t), 53.44 (q), 55.42 (d), 55.51 (d), 65.48 (t), 66.60 (s), 68.10 (t), 95.48 (t), 96.66 (t), 121.04 (t), 143.55 (s), 200.05 (s); exact mass m/z calcd for $C_{14}H_{22}O_5$ (M–CO) 270.14697, found 270.14673. **25**: FTIR (CH_2Cl_2 cast) 3483, 1695, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.00–1.10 (m, 10H), 1.20–1.25 (m, 1H), 1.75–1.85 (m, 2H), 2.40 (br s, 1H), 2.60–2.75 (m, 2H), 3.12 (br s, 1H), 3.30–3.40 (m, 6H), 3.50–3.70 (m, 7H), 4.20–4.40 (m, 4H), 4.58–4.75 (m, 4H), 4.80 (br s, 1H), 5.20 (br s, 1H), 7.35–7.45 (m, 6H), 7.60–7.70 (m, 4H), ^{13}C NMR ($CDCl_3$, 100.6 MHz) 19.22 (s), 25.04 (t), 26.21 (t), 26.92 (q), 33.62 (t), 45.83 (d), 46.36 (d), 51.86 (q), 55.26 (q), 55.38 (q), 59.07 (s), 62.82 (t), 68.87 (t), 77.49 (d), 95.94 (t), 96.88 (t), 112.94 (t), 121.03 (s), 127.71 (d), 129.68 (d), 133.87 (s), 135.62 (d), 147.09 (s), 169.15 (s); exact mass m/z calcd for $C_{36}H_{50}O_8Si$ 638.32751, found 638.33185. **26**: FTIR 3408, 2932, 1779 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (s, 10H), 1.20–1.25 (m, 1H), 1.75–1.78 (m, 2H), 2.45 (s, 1H), 2.60–2.73 (m, 4H), 3.00 (s, 1H), 3.30–3.40 (m, 6H), 3.44 (d, $J=10.2$ Hz, 1H), 3.54 (d, $J=7.4$ Hz, 1H), 3.70–3.83 (m, 2H), 4.00–4.08 (m, 1H), 4.17 (s, 1H), 4.20–4.27 (m, 1H), 4.50–4.55 (m, 2H), 4.55–4.65 (m, 2H), 4.90 (br s, 1H), 5.20 (br s, 1H), 7.30–7.40 (m, 6H), 7.60–7.64 (m, 4H); exact mass m/z calcd for $C_{31}H_{37}O_7Si$ (M–H_2O–C_4H_9) 549.23083, found 549.23249. **27**: FTIR (CH_2Cl_2, cast) 1111, 1150, 1755, 2931, 3071 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00–1.05 (m, 10H), 1.40–1.50 (m, 1H), 1.60–1.75 (m, 1H), 1.90–2.00 (m, 1H), 2.02–2.15 (m, 1H), 2.30–2.47 (m, 1H), 2.50–2.60 (m, 1H), 3.0–3.10 (m, 1H), 3.30–3.38 (m, 6H), 3.40–3.50 (m, 1H), 3.50–3.60 (m, 1H), 3.70–3.80 (m, 2H), 3.80–3.95 (m, 2H), 4.00 (br s, 1H), 4.50–4.60 (m, 4H), 5.00 (br s, 1H), 5.15–5.25 (m, 1H), 7.30–7.45 (m, 6H), 7.60–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) (rotamer mixture) δ 19.2, 22.1, 23.0, 23.1, 23.2, 26.8, 27.4, 27.60, 27.64, 27.67, 27.68, 28.9, 34.6, 35.4, 41.0, 42.8, 44.5, 45.7, 51.9, 55.2, 55.4, 56.9, 61.6, 61.7, 63.47, 63.50, 64.4, 67.7, 68.0, 69.01, 69.04, 71.2, 86.7, 86.8, 86.9, 95.8, 96.6, 112,19, 112.22, 117.0, 122.2, 123.1, 127.6, 129.62, 129.64, 133.65, 133.67, 135.5, 142.1, 145.67, 145.70, 171.3, 171.8, 174.2; exact mass m/z calcd for $C_{35}H_{46}NaO_7Si$ 629.291052, found 629.291575. **29**: FTIR (acetone, cast) 3374, 2932, 1771 cm^{-1}; ^1H NMR ($CDCl_3$–CD_3OD, 400 MHz) 5.72–5.78 (m, 1H), 4.82–4.88 (m, 1H), 4.20 (d, 1H, $J=11.7$ Hz), 4.04–4.10 (m, 2H), 3.98 (d, 1H, $J=11.7$ Hz), 3.68–3.82 (m, 2H), 3.26–3.34 (m, 1H), 2.70 (d, 1H, $J=17.0$ Hz), 2.42 (d, 1H, $J=17.1$ Hz), 2.24–2.38 (m, 2H), 2.04–2.18 (m, 2H), 1.94–2.02 (m, 1H), 1.44–1.52 (m, 1H); ^{13}C NMR (acetone-d_6, 100.6 MHz) 22.263 (t), 26.25 (t), 36.028 (t), 43.620 (d), 48.493 (s), 49.870 (t), 58.628 (t), 66.193 (t), 66.707 (t), 79.336 (d), 117.568 (d), 127.413 (s), 133.602 (s), 143.420 (s), 180.348 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{20}NaO_5$ 303.12030, found 303.11992. **30**: FTIR (CH_2Cl_2 cast) 2934, 1773, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30–1.50 (m, 1H), 1.95–2.10 (m, 1H), 2.20–2.40 (m, 2H), 2.56 (apparent dd, $J=1.84$, 14.11 Hz, 1H), 3.00 (apparent d, $J=14.11$, 1H), 3.18 (AB q, $J=18.73$ Hz, $\Delta\nu_{AB}=44.32$ Hz, 2H), 4.75–4.85 (m, 1H), 5.05–5.10 (m, 1H), 5.75–5.81 (m, 1H), 7.10 (br s, 1H), 7.15 (br s, 1H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 21.4 (t), 29.1 (t), 34.9 (d), 39.5 (t), 46.6 (s), 47.9 (t), 79.7 (d), 117.0 (s), 118.6 (d), 125.3 (s), 141.2 (d), 141.5 (d), 143.2 (s), 179.5 (s), 197.5 (d); exact mass m/z calcd for $C_{15}H_{14}NaO_4$ 281.07843, found 281.07852.