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Polyene Substrates with Unusual Methylation Patterns to Probe the Active Sites of Three Catalytic Antibodies

Geun Tae Kim, Marion Wenz, Jong Il Park, Jens Hasserodt* and Kim D. Janda*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

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Abstract—The synthesis of two tetraenes that differ in their methylation pattern from the natural substrate in lanosterol biosynthesis, 2,3-oxidosqualene, and their examination with three catalytic antibodies is described. The design of these novel, linear terpenoid structures was governed by initial results obtained from the characterization of the three catalytic antibodies. These were generated by immunization with a steroidal hapten that mimics multicyclization without the necessity for *anti*-Markovnikov additions or ring expansions. Such a reaction cascade would represent a more 'primitive' version compared to the oxidosqualene cyclization observed in lanosterol, cycloartenol and β-amyrin biosynthesis and would not require a tail-to-tail connection of the third and fourth isoprene unit as seen in squalene. The first tetraene design (A) only contains trisubstituted double bonds and hence its synthesis starts from farnesol and tris-norgeraniol. The second tetraene design (B) is considered the more precise match to the inducing hapten that generated the antibody collections by exhibiting one disubstituted double bond and its synthesis utilizes a tris-norgeraniol derivative and a symmetrical bis-allylic alcohol as key building blocks. Chromatographic comparison studies lead to the conclusion that the currently studied antibodies also produce monocyclic products from the two substrates as has been formerly observed with a squalene-derived substrate. In contrast, 2,3-oxidosqualene is not accepted by these catalysts supporting the notion that the current substrates are fully bound by recognition of both terminal functional groups.

Introduction

The field of catalytic antbodies has already procured catalysts for a variety of cationic cyclizations.[1] However, only one of them carries out a tandem cyclization.[2] It is of particular interest to extend this study to multicyclizations analogous to triterpene cyclizations. Any obtained catalyst would contribute a plethora of insights regarding active site requirements to the already building knowledge on triterpene cyclases[3] and may bear implications for the evolution of cyclase activity.[4]

Particularly, the hypothesis of 'minimal assistance'[5] by the enzyme, once initiation of multicyclization has occurred, can be verified by the catalytic antibody approach. This is due to the fact that a hapten design must be realistic and hence monoclonal antibodies generated will not be able to address every hypothetical detail of transition states along the reaction coordinate.[6] Thus, this ongoing study[7] has started with a hapten design (HA8, Fig. 1) that covers the initiation of the

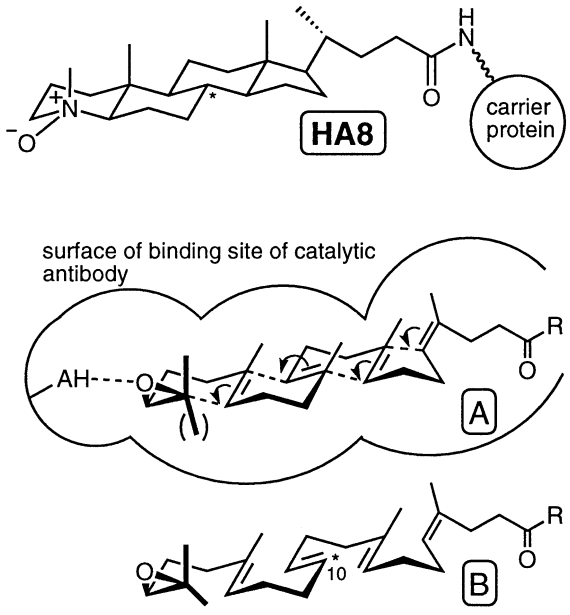

Figure 1. Different degrees of steric congruency between substrate redesigns A and B and the inducing transition state analogue/hapten showing postulated chair–chair–envelope conformations.

*Corresponding authors. Tel.: +1-858-784-2516; fax: +1-858-784-2595; e-mail: kdjanda@scripps.edu

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cascade process by introducing an *N*-oxide moiety in ring A of a steroidal framework. This should fulfill two requirements: mimicking heterolytic epoxide opening of any suitable substrate (TS analogue approach[8]) and inducing acidic amino acid residues in the vicinity that could act as proton donors for epoxide protonation (bait-and-switch approach[9]).

The main body of the hapten consists of a steroidal framework with all-*trans* connections between rings thus representing a chair–chair–chair–envelope fold of any suitable polyene substrate. This can be considered an evolutionary more 'primitive' triterpene cyclization mode compared to eucaryotic oxidosqualene cyclases that enforce chair–boat–chair folds in addition to facilitating methyl and hydrogen migrations.[3] Since the synthesis of hapten HA8[7b] was started from a suitable commercial steroid—lithocholic acid—its features were short of one methyl group to make it an ideal starting point for mimicking a 'primitive' substrate design with head-to-tail connections between the first four isoprene units thus allowing for all-Markovnikov additions. The latter contrasts oxidosqualene cyclase (OSC) and bacterial cyclases. In order to circumvent the hurdle of an *anti*-Markovnikov addition as a direct consequence of the constitution of squalene, OSC has been shown to control a five-to-six-membered ring expansion.[3]

From a collection of 25 *anti*-HA8 antibodies (produced in sufficient amounts for initial tests via standard hybridoma protocol) three catalysts (25A10, 20C7, 15D6) were selected that performed monocyclization of a squalene-derived substrate (**49**, Chart 1).[7a] These catalysts controlled initiation and formation of ring A of the steroid nucleus with pronounced preference for one substrate enantiomer (determined for 25A10), but did not foster multicyclization. However, this original substrate (**49**) cannot be considered an ideal match for the hapten design.[7a] It was therefore concluded that more refined substrates had to be created in order to test the hypothesis that the three catalysts were not able to enforce a productive fold of the hydrocarbon chain of **49**.

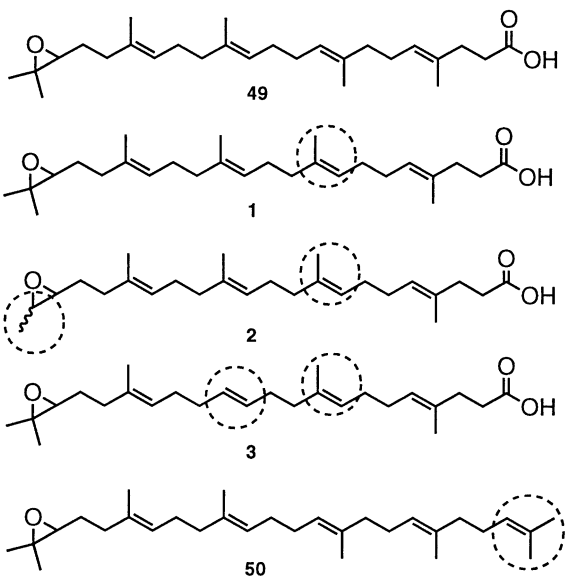


Chart 1. Dashed circles indicate deviations from the original substrate **49**.

Two general polyene substrate designs were targeted in this study differing only in their methylation pattern. Design A (Fig. 1) displays four isoprene units with head-to-tail connections before being linked to the fifth by a tail-to-tail link thus giving rise to all-Markovnikov additions in a reaction leading to a 6,6,6,5-steroidal framework. Substrates adhering to this design may cyclize more readily under the influence of the current antibodies, since high-energy *anti*-Markovnikov additions or ring expansions are not required.

Design B lacks the 10-methyl substitutent that is not accounted for in the hapten design. This should eradicate any doubts about anti-HA8 antibody combining sites not being able to accommodate an extra methyl group. However, such a design implies a somewhat higher energy barrier for the second electrophilic double-bond addition since this double bond is only disubstituted.

Results and Discussion

Substrate design A was planned to lead to two synthetic targets differing slightly in the number of methyl substituents on the epoxide trigger group (**1** and **2**; Fig. 2). The retrosynthetic analysis led to two starting materials, farnesol and geraniol. Both molecules provide all isoprenoidal double bonds in configurational purity and could conceivably be fused using allylic cross-coupling methodology. In contrast, design B in the form of the synthetic target **3** carries a disubstituted double bond. Thus farnesol was ruled out as a suitable starting mat-

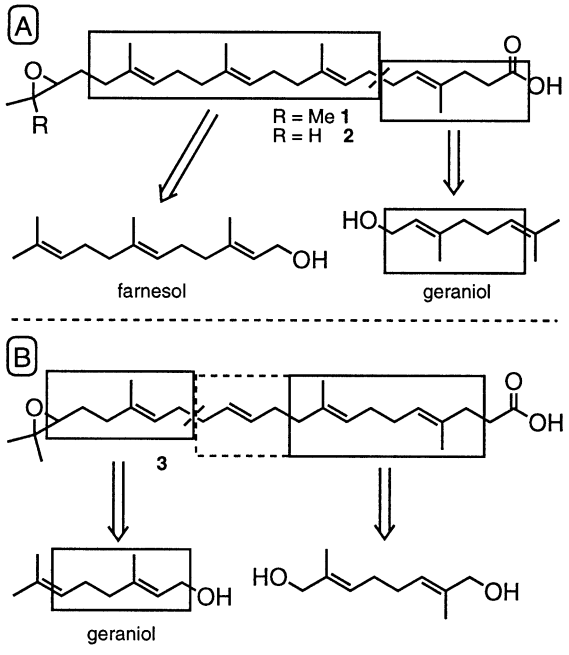
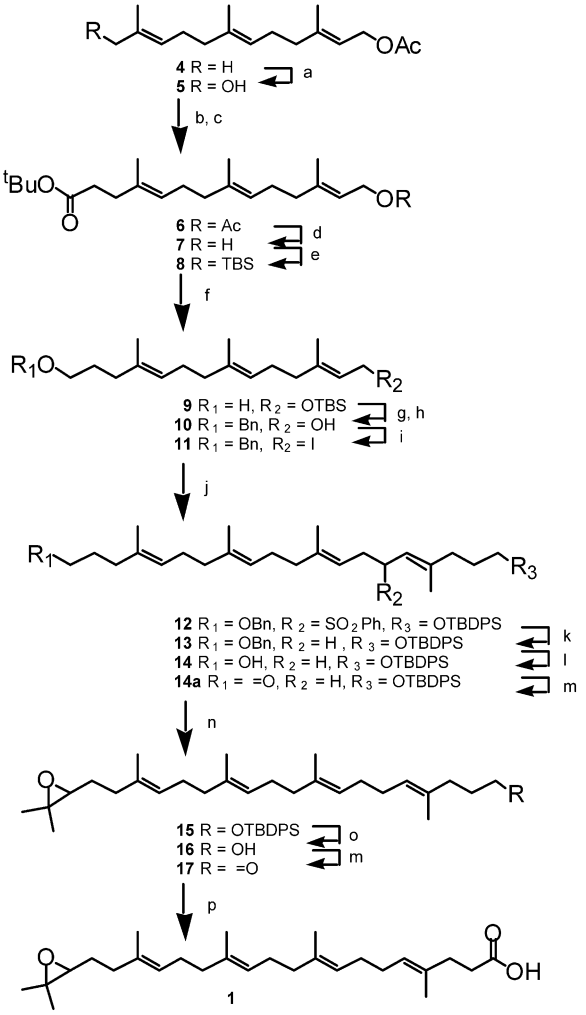


Figure 2. Fractionation of substrate prototypes A and B into suitable synthetic starting materials.

erial in favor of a purely synthetical, symmetrical synthon carrying two allylic alcohol moieties (Fig. 2). This building block was planned to be elongated by a double bond-bearing four-carbon unit before coupling to the synthon derived from geraniol. The essential epoxide moiety was to be installed as late as possible due to its instability. Based on this consideration the polyenic nature of the target molecule made sulfur ylid chemistry the method of choice.

The synthesis of substrate **1** adhering to design A (Scheme 1) started with the regioselective SeO_2/*t*BuOOH oxidation of farnesol[10] acetate (**4**) to the mono-acetylated bis-allylic alcohol **5**. Iodination of the unprotected hydroxyl group followed by reaction with deprotonated *t*-butyl acetate gives acetate **6**. Protecting groups were next swapped from acetate to *t*-butyl-

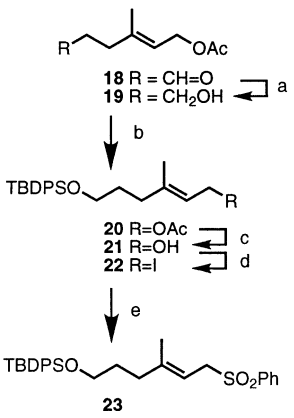


Scheme 1. (a) SeO_2, *t*-BuOOH; (b) PPh_3, I_2, imidazole, CH_3CN/Et_2O (2:3); (c) *t*-butyl acetate, HMPA, lithium cyclohexylisopropylamide, THF, −78 °C, **7** (66%) and **6** (11%); (d) MeOH, K_2CO_3, rt, 81%; (e) TBSCl, imidazole, DMF, 83%; (f) $LiAlH_4$, THF, 83%; (g) BnBr, *n*-Bu_4NI, NaH, THF/DMF (4:1); (h) *n*-Bu_4NF, THF (98%); (i) PPh_3, I_2, imidazole, CH_3CN/Et_2O (2:3), 81%; (j) **23**, *n*-BuLi, THF, −78 °C, 83%; (k) Pd(dppp)Cl_2, $LiEt_3BH$, THF, 0 °C, 84%; (l) lithium naphthalide, THF, −25 °C, 100%; (m) SO_3Py, DMSO, Et_3N, CH_2Cl_2, 81%; (n) Ph_2Si–$PrBF_4$, *t*-BuLi, THF, −78 °C; (o) *n*-Bu_4NF, THF, 85% over two steps; (p) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-butanol, H_2O, 68%.

dimethylsilyl ether followed by LAH reduction. The resulting alcohol **9** was benzylated to provide a protecting group orthogonal to the silyl ether. The latter was subsequently removed and the resulting allylic alcohol **10** iodinated, followed by an allylic cross-coupling[11] with synthon **23** (an allylic sulfone derived from geranyl actetate; Scheme 2) in excellent yields. It should be noted that other allylic cross-coupling techniques based on allylic barium reagents[12] and allyl thioethers[13] failed to give any product.[14] However, the subsequent removal of the sulfone substituent turned out to be an unexpected challenge. Typical techniques using Li/NH_3, Li/$EtNH_2$, and lithium naphthalide[15] failed to give homogenous products; 5% Na/Hg/MeOH provided **13** as a mixture (4:1, 79% yield) with a minor, isomerized product exhibiting a disubstituted double bond due to 1,2-migration. Finally, a palladium-catalyzed reduction with superhydride™ (lithium triethyl borohydride) produced the desired key intermediate **13** in 84% yield.[16] Here, double-bond migration is avoided as the bulky hydride preferentially attacks on the less hindered carbon of the intermediate palladium–allyl complex. Subseqent removal of the benzyl group via the very mild lithium–naphthalide method followed by $PyrSO_3$ oxidation[17] to the aldehyde prepared the molecule for establishment of the dimethylepoxide moiety in **15** with the sulfur ylid derived from diphenyl *i*-propyl sulfonium tetrafluoroborate.[18] Final steps consisted of silyl group removal and the stepwise oxidation of alcohol **16** to the corresponding acid **1**, the target compound, by use of $PyrSO_3$ and $NaClO_2$.[19] This stepwise oxidation procedure gave superior yields over direct methods using stronger oxidants like Ag_2O or pyridinium dichromate in DMF.

Epoxy acid **2** (the nor derivative of **1**) was obtained by replacing diphenyl *iso*-propyl sulfonium tetrafluoroborate with diphenyl ethyl sulfonium tetrafluoroborate (Scheme 3) in the reaction with aldehyde **26**. Subsequent steps are identical to those shown in Scheme 1.

The synthesis of substrate **3** (Fig. 2), as based on design B again consisted of fusion of two fragments via coupling of an allylic sulfone and an allylic halide. Synthesis of the sulfone fragment **30** was carried out as follows



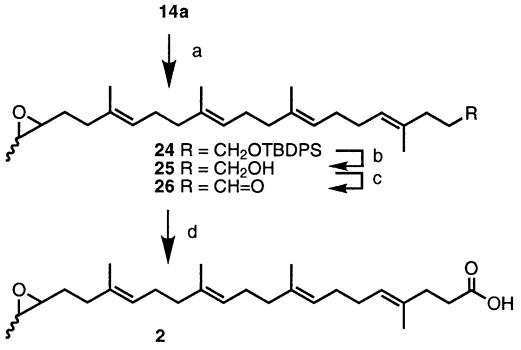
Scheme 2. (a) $NaBH_4$; (b) TBDPSCl, imidazole, DMF; (c) MeOH, K_2CO_3, 83% over two steps; (d) PPh_3, I_2, imidazole, CH_3CN/Et_2O (2:3), 62%; (e) $PhSO_2Na$, DMF, 92%.

(Scheme 4): Aldehyde **18**, derived from geraniol, was prepared as previousely described[20] and protected under standard conditions to form the acetal **27**. Its allylic acetate moiety was then cleaved under standard conditions and the resulting alcohol **28** was converted into the allylic bromide **29** via the mesylate by subsequent treatment with LiBr.[21] Finally, sulfone **30** was formed under mild conditions by adding the sodium salt of the corresponding sulfinic acid.[22]

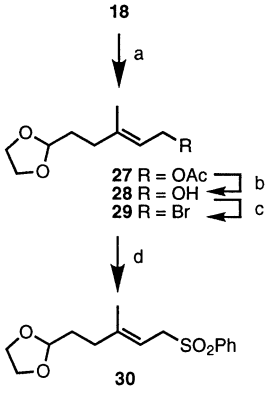
For the synthesis of the symmetrical unit of the allylic halide fragment, the stereochemically pure *E,E*-bisallylic alcohol **34** was constructed starting with titanium-mediated γ-dimerization[23] of the mixed *E*/*Z*-isomers of silylvinylketene acetal **32**, obtained from methyl tiglate (**31**) (Scheme 5). This highly stereospecific procedure proved to be a very efficient process, superior to the alternative double-Wittig reaction starting from succinic aldehyde that is known to yield an undesired 9:1 mixture of the two *E*/*Z* isomers.[24] Clean 1,2-reduction of the crystalline unsaturated diester **33** with DIBAH[25] afforded the pure key intermediate **34**, bearing the correct stereochemistry as confirmed by NOE experiments. Compound **34** was then monosilylated using the sodium monoalkoxide methodology[26] to give **35**, and brominated to yield **36**.

Further 3-carbon elongation was achieved by reacting allylic bromide **36** with the in situ-generated 3-lithio derivative of 1-TMS-propyne[27] yielding the corresponding 1-ene-5-yne system **37**.[28] The propargylic silane was deprotected selectively in the presence of the TBS–ether under mildly basic conditions using K_2CO_3 in MeOH.[29] Further deprotonation of the resulting primary alkyne **38** with *n*-BuLi, to generate the lithium acetylide in situ, and its subsequent reaction with *p*-formaldehyde afforded the propargylic alcohol **39**,[30] which was selectively transformed into the corresponding (*E*)-allylic alcohol **40** by treatment with Red-Al®.[31] This alcohol was again transformed into its bromide **41** (vide supra).

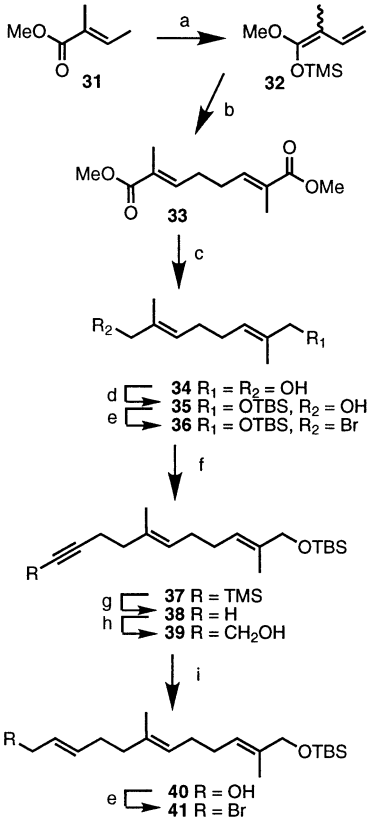
The allylic sulfone **30** was coupled to the allylic bromide **41** via a deprotonation-addition sequence to give the secondary allylic sulfone **42** (Scheme 6). Subsequent reductive desulfonylation was carried out using superhydride® and a catalytic amount of $Pd(OAc)_2$/dppp[32] to afford the corresponding disubstituted olefin **43** in a highly regio- and stereoselective manner.[33] The TBS ether remains uncleaved during this step if the reduction is stopped as soon as desulfonylation is complete. In order to extend the polyenic carbon backbone, TBAF deprotection was followed by dehydrative alkylation with triethyl methanetricarboxylate (TEMT) under *Mitsunobu* conditions[34] to form the two carbon-elongated compound **45**. Subsequent double decarboxylation was carried out under *Krapcho*-like conditions[35]



Scheme 3. (a) Ph_2SEtBF_4, *t*-BuLi, THF, −78 °C; (b) *n*-Bu_4NF, THF, 21% over two steps; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butaene, *t*-butanol, H_2O, 83% over two steps.



Scheme 4. (a) Ethylene glycol, *p*-TosOH, toluene, reflux, 70%; (b) K_2CO_3, H_2O/MeOH, rt, 96%; (c) MsCl, NEt_3, CH_2Cl_2, −40 °C; LiBr, THF, rt; (d) $PhSO_2Na$, DMF, 0 °C, 80% over two steps.

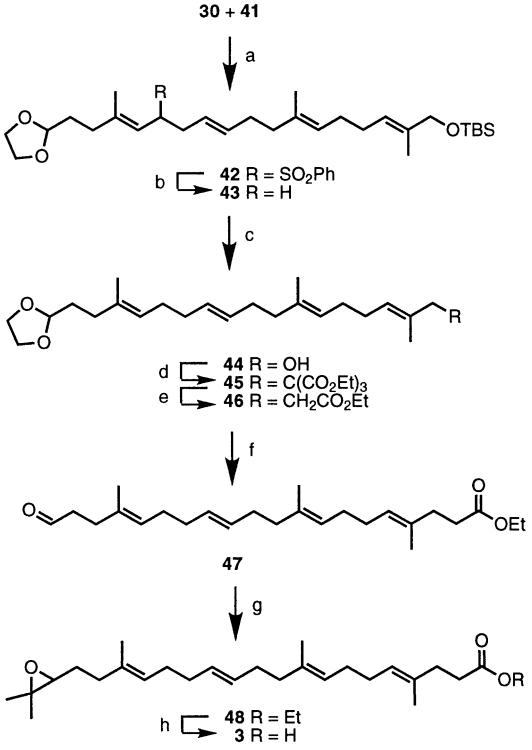


Scheme 5. (a) LDA, THF, −65 °C; TMSCl, THF, rt, 84%; (b) $TiCl_4$, CH_2Cl_2, 0 °C, 63%; (c) DIBAL, CH_2Cl_2, −78 °C, 94%; (d) NaH, TBSCl, THF, rt, 55%; (e) (i) MsCl, NEt_3, CH_2Cl_2, −40 °C; (ii) LiBr, THF; (f) 1-TMS-propyne, *n*-BuLi, TMEDA, 0 °C, 67% over two steps; (g) K_2CO_3, MeOH, rt, 82%; (h) CH_2O, *n*-BuLi, THF, −60 °C, 65%; (i) *Red-Al*, toluene, −78 °C, 69%.

by using excess LiCl as the neutral nucleophile to afford the monoester **46**. The epoxide moiety was introduced by cleavage of the acetal to give aldehyde **25**, and subsequent treatment with the sulfur ylid generated from *iso*-propyl diphenyl sulfonium tetrafluoroborate and *t*-BuLi.[36] Saponification of the ethylester moiety of epoxide **48** under standard conditions provided the desired carboxylic-acid substrate **3**.

The thus obtained substrates were tested with catalytic antibodies HA8-25A10, -20C7, -15D6 and a non-related control antibody (cab). This assay, that employs the surfactant TWEEN 80 to solubilize the hydrophobic substrates in phosphate buffer, was previously used with substrate **49** (Chart 1) to obtain an initial characterization of these catalysts.[7a] While extraction with for example methyl *t*-butyl ether and subsequent TLC analysis gave a valuable qualitative picture of the reaction, a more quantitative analysis of the extracts using gas chromatography was not feasible. It was found that the substrate carboxylic acids and their corresponding products did not show sufficient volatility, even after methyl ester formation. However, since it was desirable to detect products directly in the reaction mixture to avoid any alteration of the product composition through extraction and derivatization steps, liquid chromatography was determined to be the superior method as it allows for direct analysis of the reaction mixture. Thus, HPLC coupled with mass spectrometry detection (LCMS) was used throughout this work because of the highly sensitive detection of products whose low chromogenicity prohibits precise spectrophotometric detection. In order to obtain chromatograms with the degree of resolution depicted in Figure 3 only selected masses [selected ion monitoring (SIM)] were monitored. These consisted of the major signals obtained by initial scans of the respective substrates between 100 and 800 μ *and* masses obtained by the addition of 18 μ analogous to a H_2O addition as part of one of the two termination pathways of cationic cyclization in aqueous media. Since a rearrangement reaction is studied, it was expected that all products would be detectable by this method, albeit with varying response levels.

According to these LCMS analyses (Table 1 and Fig. 3), antibody catalysts 25A10, 20C7 and 15D6 did not show marked difference in product formation with the new substrate structures **1** and **3**. The product signals with retention times of 5.05, 4.75 and 4.95 min for the reactions with **1** and **3** and the original substrate **49**, respectively, with all three catalysts assumed virtually identical



Scheme 6. (a) *n*-BuLi, THF, −78 °C, 91%; (b) $LiBHEt_3$, $Pd(OAc)_2$, dppp, THF, 0 °C, 83%; (c) TBAF, SiO_2, THF, −50 °C→rt, 89%; (d) DEAD, PPh_3, TEMT, Et_2O, rt, 83%; (e) LiCl, H_2O/DMSO, 189 °C, 64%; (f) *p*-TsOH, H_2O/acetone, 50 °C, 77%; (g) $[Ph_2(i\text{-prop})S]^+BF_4^-$, *t*-BuLi, THF, −78 °C, 62%; (h) NaOH, H_2O/MeOH, rt, 99%.

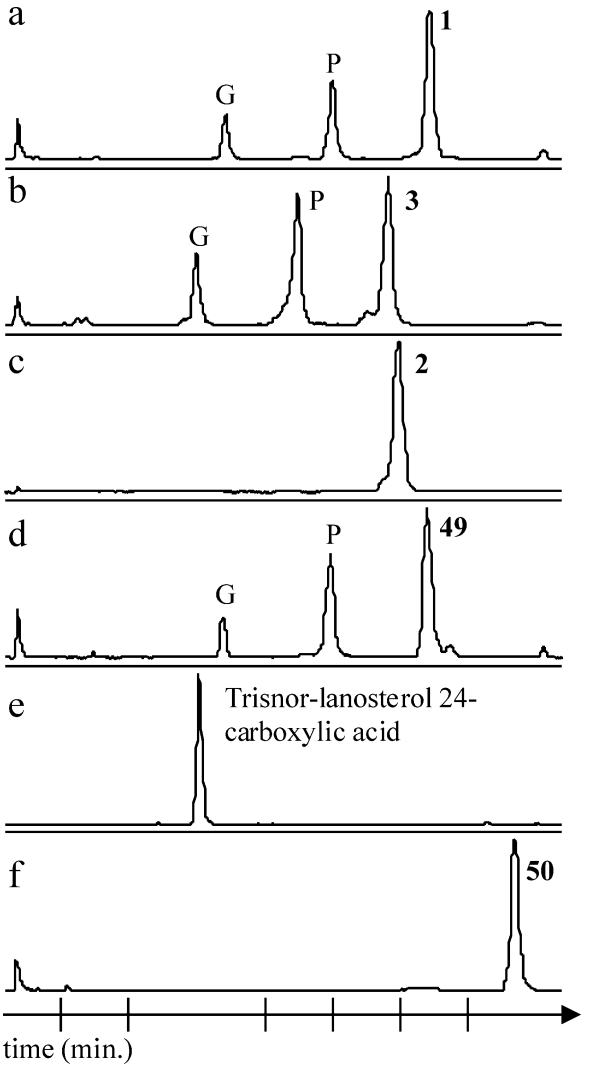


Figure 3. P = monocyclic product, G = glycol (hydrolysis), chromatograms a–e were acquired using same mobile phase gradient; for f the gradient had to be shifted to more apolar mixtures. Conditions: 10 μM IgG 25A10, 400 μM substrate, 50 mM phosphate buffer, pH 7.0, 22 °C, 135 h.

positions with regard to the substrate peak (6.5, 6.05 and 6.45 min, respectively) making monocyclization for these altered substrate structures the most likely reaction outcome in congruency with the established product spectrum from **49**.[7a] A multicyclized structure like the tetracylic carbocylic acid derived from lanosterol, which is a possible cyclization product from **49** by an OSC-like cyclase, elutes 1.8 min earlier than the monocyclic antibody products (chromatogram e; Fig. 3). It even elutes 0.6 min earlier than the glycol (peak G at 3.25 min in chromatograms a, b, and d) formed by background hydrolysis from the original substrate **49** despite the fact that it carries only two polar functional groups (one hydroxyl and one carboxyl) instead of three (two hydroxyls and one carboxyl). This illustrates the considerable difference in interaction with the immobile phase resulting from the largely differing rigidity of monocyclic versus tetracylic systems. However, chromatograms a, b and d (Fig. 3) show distinctive minor product components with retention times in the area where dihydroxylated species may be expected resulting from a termination pathway that consists of water addition to the terminal carbocation. The individual mass spectra support this observation. Due to the low abundance of these minor products, actual isolation and NMR characterization was not attempted.

Table 1 provides a crude determination of rates of product (monocyclic) formation from substrates **1**, **2**, **3**, **49** with all three catalytic antibodies and a non-related control antibody. The applied substrate concentration (400 μM) can be regarded as comparatively low for these catalysts since attempts to reach their saturation under the current assay conditions has been impossible. At least part of the reason may be that $[S]_0$ may only be an apparent substrate concentration due to the fact that the hydrophobic substrates are mostly contained in the micelle interior (TWEEN 80!). It can be assumed that their respective partition constant for diffusion into the aqueous exterior where the antibody catalyst resides is rather low. Consequently, this is a situation of *low* substrate concentration where the Michaelis–Menten equation assumes the following simpler form:[37] $v = k_{cat}/K_M$ [E][S], where [E] is the concentration of free or unbound enzyme. Since [E] and [S] where held constant in this study (Table 1), the deviations of the shown rates have to be attributed to differences in the specificity constant k_{cat}/K_M. Thus, the antibodies show improved molecular recognition of the transition state of substrate **3** by virtue of its largest rate. This may serve as an indication that indeed substrate design B carrying no methyl substituent at C10 has superior congruency with the hapten structure.

Table 1. Crude rates of monocyclic product formation (relative to total amount of initial substrate and products expressed in peak area percent after 135 h reaction time)[a]

	1 (399, 417, 433, 439, 455)[b]	**3** (385, 403, 421, 425, 443)[b]	**2** (385, 403, 425)[b]	**49** (399, 417, 433, 439, 455)[b]
25A10	24.8	35.3	0.7	30.4
20C7	3.5	18.2	1.5	2.4
15D6	0.5	11.9	0.4	21.2
Control antibody	0	0	0	0

[a]Conditions: 10 μM antibody (IgG), 400 μM *racemic* substrate, 50 mM phosphate buffer, pH 7.0, 22 °C, 0.1% TWEEN 80, 135 h.
[b]Ions monitored.

Substrate **2** (a mixture of two diastereomeric sets of enantiomers) exhibits the same methylation pattern as **1**. It was hoped that by exclusion of one of the two methyl substituents on the epoxide moiety one may prevent any repulsive interactions with the antibody combining site that may be prevalent in the interaction with substrates **49**, **1**, and **3** due to a less space-consuming hapten (Fig. 1). However, any positive effects resulting from this design alteration were overcompensated by the inherently lower basicity of a disubstituted epoxide moiety which results in a marked drop in reactivity as is evident from Figure 3, chromatogram c. This phenomenon has been observed during the probing of yeast oxidosqualene cyclase with similar trigger group variations.[38] That a comparable mode of reaction is still promoted by the current antibodies can be seen from the low-intensity peak at 4.59 min (visible only after zooming in on the baseline of chromatogram c) which corresponds to the peak at 4.95 min (monocyclic product[7a]) in chromatogram d (Fig. 3).

The substrate **3**, deprived of one of the four methyl groups present in **49** and **1**, shows a more pronounced formation of dihydroxylated species. It may be speculated that this has resulted from the substrate leaving more room for water molecules in the active site. Table 1 reports relative velocities for monocyclic product formation by all three catalytic antibodies. While IgG 25A10 turns out to be the most proficient catalyst, all three antibodies exhibit almost identical product spectra/peak distributions. This may indicate a close genetic relation as has been observed with other catalytic antibodies obtained by standard hybridoma protocol.[39]

Importantly, parallel experiments carried out with 2,3-oxidosqualene (**50**) (Chart 1, Fig. 3), did not show any activity with the current antibody catalysts. This illustrates how successfully the hapten design (Fig. 1) instructed the antibodies to recognize and bind the entirety of these linear and conformationally quite mobile molecules including the carboxylic-acid tail.

To obtain some initial insight into the catalytic mechanism of antibody 25A10, a pH rate profile with substrate **49** (obtainable in largest amounts in this study) was constructed. The bell-shaped dependency indicates the presence of two ionizable groups being involved in the rate-determining step of this catalytic antibody.[40] The optimum performance was observed at pH 6.3, rather close to the value seen with natural triterpene cyclases.[41] The crystal structure of squalene-hopene cyclase has revealed the presence of an aspartic acid residue that—for various structural reasons and because it was in close contact with the aminoxide moiety of a bound inhibitor[42]—was made resonsible for initiation by epoxide or double bond protonation. Whether such an aspartate or glutamate is a likely

candidate for one of these residues has to await a detailed k_{cat}–pH dependency study for further support even though such interpretations generally bear various pitfalls.[43] Substrate **49** carries an ionizable carboxylic acid group but the impact of its pK_a of ca. 4–5 on the present pH study is believed to be small since at most studied pH values the substrate exists in its anionic form.

Conclusion

The substrate structures presented in this contribution have been chosen to further probe the active site of three catalytic antibodies raised against a steroidal hapten. The hypothesis that a higher congruency of substrate and hapten structure would enable the catalysts to enforce a more productive conformation of the polyene chain for multicyclization could not be verified. In light of the current findings, the three antibodies appear to lack the capability to properly align the second double bond to the first to accomplish bicyclization. Nonetheless, these antibodies have been taught to stabilize the initial TS and to bind the entire length of the substrates most probably in a tightly folded fashion in congruency with the compactness of the hapten design. The steroidal framework of the hapten makes a pseudo-chair–chair–chair fold likely while precision of this fold has apparently not been accomplished. The pH rate dependency and optimum of antibody 25A10 also suggests the presence of an acidic residue characteristic for triterpene cyclases.

Considering the complexity of the task of multicyclization, the required fine tunings to achieve it were left to a considerable extent to the diversity of the immune response rather than to hapten design. Thus, it appears paramount to significantly increase the pool of possible candidates from the currently tested set of 25 monoclonal antibodies that were obtained by traditional hybridoma protocols. This may either be done by variegating the already exisiting catalytic machinery of the current catalytic antibodies by cloning and various directed evolution techniques or by deriving an antibody library from the immunization with hapten HA8 (Fig. 1).

Experimental

General procedures

If not stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-600, 500 instrument at 600, 500 and 150, 125 MHz, repectively. Chemical shifts (δ) are given in ppm relative to $CHCl_3$ in $CDCl_3$ (7.27 ppm, ^{1}H: 77.00 ppm, ^{13}C). Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), and m (multipet). High-resolution mass spetra (HRMS) were recorded at The Scripps Research Institute on VG ZAB-ZSE mass spectrometer.

All reactions were monitored by thin-layer chromatography (TLC), using 0.25 mM Merck Silicagel Glass Plates (60F-254), fractions being visualized by UV light, phosphomolybdic acid solution (or other staining solutions as indicated) with subsequent heat application. Column chromatography was carried out with Mallinckrodt SilicAR 60 silicagel (40–63 μM). Reagent grade solvents for chromatography were obtained from Fisher Scientific. Reagent and anhydrous solvents were obtained from Aldrich Chemical Co. and used without further purification. All reactions were carried out under anhydrous conditions and an atmosphere of argon, unless otherwise noted. Reported yields were determined after purification to homogenous material.

Ester (7). To a solution of **5** (2.69 g, 9.60 mmol), imidazole (981 mg, 14.4 mmol) and triphenylphosphine (3.78 g, 14.4 mmol) in a 2:3 mixture of acetonitrile and Et_2O (50 mL) was added iodine (3.65 g, 14.4 mmol) portionwise over 30 min with 10 min intervals at 0 °C. After 1 h, excess iodine was quenched with 15% sodium thiosulfate and the mixture was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:20) to afford the corresponding iodide (2.98 g, 80%) as a colorles oil.

n-BuLi (10.15 mL, 2.5 M in hexane, 25.37 mmol) was added slowly to a solution of *N*-isopropylcyclohexylamine (4.17 mL, 25.38 mmol) in THF (21 mL) at 0 °C and stirring was continued at this temperature for 20 min before cooling to −78 °C. The mixture was slowly treated with freshly distilled *t*-butyl acetate over 15 min. Stirring was continued for 30 min before the above iodide (3.30 g, 8.46 mmol) in THF (10 mL) was added through a double-tipped needle. After 10 min, the reaction mixture was treated with hexamethylphosphoramide (HMPA, 4.41 mL). After a further 30 min, the reaction was quenched with satd NH_4Cl. The resulting mixture was warmed to room temperature and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified using column chromatography (EtOAc/hexane, 1:20→1:5) to give 1.883 g (66%) of 7 and 377 mg (11%) of **6** as colorless oils. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.55 (3H, s), 1.56 (3H, s), 1.64 (3H, s), 1.92–1.94 (2H, m), 1.99–2.09 (6H, m), 2.19–2.28 (4H, m), 4.11 (2H, d, $J = 6.9$ Hz), 5.05–5.36 (2H, m), 5.37–5.38 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.88, 15.94, 16.23, 26.19, 26.46, 28.06, 28.09, 34.35, 34.77, 39.48, 59.30, 80.01, 123.39, 123.86, 124.74, 133.43, 135.11, 139.49, 172.90; HRMS (MALDI-FTMS) calcd for $C_{21}H_{36}O_3$ ($M + Na^+$) 359.2562; found 359.2554.

Conversion of acetate 6 to 7. Acetate **6** (418 mg, 1.10 mmol) was stirred with K_2CO_3 (15 mg, 0.11 mmol) in MeOH (5 mL) at room temperature After 15 h, H_2O (20 mL) was added and the mixture was extracted with Et_2O. Solvent evaporation followed by column chromatography (EtOAc/hexane, 1:4) gave 303 mg (81%) of **7** as a colorless oil.

Alcohol (9). To a solution of **7** (2.18 g, 6.49 mmol) and imidazole (1.06 g, 15.5 mmol) in DMF (20 mL) was

added *t*-butyldimethylsilyl chloride (1.17 g, 7.79 mmol) at 0 °C. After 2 h, H_2O (50 mL) was added and the mixture was extracted with Et_2O (3×50 mL). The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:40) to give 2.43 g (83%) of **8** as a colorless oil.

8 (2.74 g, 6.09 mmol) in Et_2O (20 mL) was added dropwise to a solution of lithium aluminum hydride (346 mg, 9.11 mmol) in Et_2O (20 mL) over 15 min at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h and cooled in an ice bath. H_2O (0.35 mL) was added carefully over 10 min before the addition of 15% NaOH (0.35 mL) and H_2O (1.05 mL). This resulted in a grain-like texture of the solid that was filtered off through Celite. The filtrate was evaporated to afford an oil which was purified by column chromatogaphy (EtOAc/hexane, 1:4) to give 2.21 g (83%) of **9** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 1.40 (1H, brs), 1.57 (3H, s), 1.58 (3H, s), 1.60 (3H, s), 1.61–1.66 (2H, m), 1.94–2.00 (4H, m), 2.01–2.09 (6H, m), 3.60 (2H, t, J = 6.5 Hz), 4.17 (2H, d, J = 5.7 Hz), 5.07–5.13 (2H, m), 5.27–5.29 (1H, m), ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.05, 15.84, 15.94, 16.34, 18.42, 26.00, 26.25, 26.48, 30.70, 35.97, 39.51, 39.59, 60.34, 62.79, 124.09, 124.35, 124.73, 134.58, 134.99, 136.86; HRMS (MALDI-FTMS) calcd for $C_{23}H_{44}SiO_2$ ($M + Na^+$) 403.3008; found 403.3000.

Benzyl ether (10). Benzyl bromide (0.86 mL, 7.27 mmol) was added to a solution of **9** (1.393 g, 3.65 mmol), sodium hydride (219 mg, 60% in a mineral oil, 5.47 mmol) and *n*-tetrabutylammonium iodide (67 mg, 0.18 mmol) in a 4:1 mixture of THF and DMF at 0 °C. After 20 min the mixture was warmed to room temperature and stirred for 10 h. Satd NH_4Cl was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc/hexane, 1:20) to afford the corresponding benzyl ether that was contaminated with benzyl bromide.

The crude benzyl ether was stirred with *n*-tetrabutylammonium fluoride (5.5 mL, 1.0 M in THF, 5.5 mmol) in THF (8 mL) at room temperature After 12 h, the mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc/hexane, 1:8→1:5) to give 1.284 g (98%) of **10** over two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (6H, s), 1.65 (3H, s), 1.68–1.72 (2H, m), 1.94–2.11 (10H, m), 3.43 (2H, t, J = 6.4 Hz), 4.11 (2H, d, J = 6.1 Hz), 4.48 (2H, s), 5.07–5.11 (2H, m), 5.36–5.42 (1H, m), 7.24–7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.85, 15.92, 16.20, 26.19, 26.45, 27.92, 35.94, 39.46, 39.55, 59.22, 69.94, 72.79, 123.36, 123.77, 124.39, 127.41, 127.56, 128.26, 134.31, 135.17, 138.52, 139.40; HRMS (MALDI-FTMS) calcd for $C_{24}H_{36}O_2$ ($M + Na^+$) 379.2613; found 379.2610.

Sulfone (12). To a solution of **10** (1.284 g, 3.06 mmol), imidazole (368 mg, 5.41 mmol) and triphenylphosphine (1.419 g, 5.41 mmol) in CH_3CN/Et_2O 2:3 (25 mL) was added iodine (1.373 g, 5.41 mmol) portionwise over 30 min with 10 min intervals at 0 °C. After 30 min, the excess iodine was quenched with 15% sodium thiosulfate and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:20) to give 1.36 g (81%) of **11** as a colorless oil.

n-BuLi (1.74 mL, 4.35 mmol) was added dropwise to **23** (2.15 g, 4.37 mmol) in THF (15 mL) at −78 °C. After 1 h, **11** (1.36 g, 12.91 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After the mixture was stirred for 7 h at −78 °C, satd NH_4Cl was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:8) to give 2.02 g (83%) of **12** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.13 (3H, s), 1.47–1.50 (2H, m), 1.54 (3H, m), 1.56 (3H, s), 1.58 (3H, s), 1.65–1.70 (2H, m), 1.91–2.05 (12H, m), 2.28–2.36 (1H, m), 2.84–2.88 (1H, m), 3.42 (2H, t, J = 6.4 Hz), 3.57 (2H, t, J = 6.0 Hz), 3.70 (1H, dt, J = 2.8, 10.4 Hz), 4.47 (2H, s), 4.92–4.97 (2H, m), 5.02–5.09 (2H, m), 7.24–7.45 (13H, m), 7.53–7.57 (1H, m), 7.63–7.64 (4H, m), 7.79–7.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.86, 15.92, 16.33, 16.47, 19.15, 26.28, 26.55, 26.60, 26.80, 27.96, 30.77, 35.91, 35.99, 39.64, 39.67, 63.35, 64.77, 69.97, 72.82, 116.94, 118.46, 123.83, 124.39, 127.42, 127.56, 127.59, 128.29, 128.62, 129.04, 129.56, 133.24, 133.85, 134.37, 135.09, 135.47, 138.01, 138.60, 138.67, 145.03; HRMS (MALDI-FTMS) calcd for $C_{53}H_{70}O_4SSi$ ($M + Na^+$) 853.4662; found 853.4673.

Benzyl ether (13). Lithium triethylborohydride (super hydride™) (5.34 mL, 5.34 mmol) was added portionwise over 2 h to a solution of **12** (2.02 g, 2.43 mmol) and bis(diphenylphosphino)propanepalladium(II)dichloride [(dppp)$PdCl_2$)][44] (72 mg, 0.122 mmol) in THF (26 mL) at 0 °C. After the mixture was stirred for 12 h, satd NH_4Cl was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:40) to afford 1.413 g (84%) of **13** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.54 (3H, s), 1.56 (9H, s), 1.59–1.73 (4H, m), 1.96–2.08 (16H, m), 3.45 (2H, t, J = 6.6 Hz), 3.65 (2H, t, J = 6.6 Hz), 4.49 (2H, m), 5.12–5.13 (4H, m), 7.24–7.41 (11H, m), 7.66–7.68 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.89, 15.96, 16.00, 16.04, 19.21, 26.65, 26.69, 26.86, 28.02, 28.25, 28.28, 30.97, 35.81, 36.04, 39.68, 39.75, 63.60, 70.04, 72.86, 124.25, 124.29, 124.38, 124.58, 127.44, 127.55, 127.59, 128.31, 129.45, 134.15, 134.32, 134.76, 134.84, 135.10, 135.56, 138.70; HRMS (MALDI-FTMS) calcd for $C_{47}H_{66}O_2Si(M + Na^+)$ 713.4730; found 713.4721.

Alcohol (14). Lithium naphthalide solution (0.3 M) was prepared as follows. Granulated lithium (51 mg, 7.34 mmol) was immersed in MeOH to clean the surface,

rinsed with anhydrous THF, and then added to a solution of naphthalene (926 mg, 7.23 mmol) in THF (24 mL) under Ar at room temperature. The mixture was stirred vigorously for 3 h resulting in a dark green solution that was immediately used for the following.

Lithium naphthalide (5 mL, 0.3 M in THF, 1.5 mmol) was added to a solution of **13** (500 mg, 0.723 mmol) in THF (5 mL) at −25 °C. After 30 min, satd NH_4Cl was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:20→1:6) to afford 449 mg (100%) of **14** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.55 (3H, s), 1.60 (3H, s), 1.64–1.65 (4H, m), 1.97–2.05 (16H, m), 3.59–3.64 (4H, m), 5.10–5.14 (4H, m), 7.34–7.42 (6H, m), 7.75–7.77 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.83, 15.93, 15.95, 16.03, 19.19, 26.54, 26.64, 26.83, 28.22, 28.25, 30.66, 30.92, 35.79, 35.98, 39.62, 39.72, 62.80, 63.58, 124.24, 124.35, 124.37, 124.80, 127.54, 129.45, 134.09, 134.56, 134.74, 134.77, 135.09, 135.54; HRMS (MALDI-FTMS) calcd for $C_{40}H_{60}O_2Si$ ($M+Na^+$) 623.4260; found 623.4258.

Alcohol (16). Pyridine–sulfur trioxide complex (180 mg, 1.13 mmol) in DMSO (1.5 mL) was added to a solution of **14** (100 mg, 0.166 mmol) and triethylamine (0.24 mL, 1.72 mmol) in CH_2Cl_2 at 0 °C. After 2 h, H_2O was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:20) to give 90 mg (90%) of the aldehyde **14a** as a colorless oil.

t-BuLi (1.7 M in pentane) was added dropwise to a solution of isopropyldiphenyl-sulfonium tetrafluoroborate in THF at −78 °C. The above aldehyde in THF was added and the mixture was stirred for 30 min, before being quenched with sat. NH_4Cl. The combined ethereal extracts of this mixture were dried over $MgSO_4$ and concentrated under reduced pressure. The remaining residue was purified by column chromatography to give **15**.

The silyl ether **15** was stirred with *n*-tetrabutylammonium fluoride in THF at room temperature After 12 h, water was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The remaining oil was purified by column chromatography to afford **16** (85% over two steps). ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.27 (3H, s), 1.56 (6H, s), 1.58 (6H, s), 1.60–1.66 (4H, m), 1.94–2.06 (15H, m), 2.09–2.14 (1H, s), 2.67 (1H, t, $J=6.6$ Hz), 3.59 (2H, t, $J=6.2$ Hz), 5.07–5.15 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.86, 15.95, 15.96, 16.01, 18.69, 24.86, 26.58, 26.59, 27.39, 28,12, 28.18, 30.70, 35.97, 36.25, 39.59, 39.69, 58.37, 62.74, 64.20, 124.10, 124.29, 124.75, 124.87, 133.92, 134.72, 134.74, 135.18; HRMS (MALDI-FTMS) calcd for $C_{27}H_{46}O_2$ ($M+Na^+$) 425.3390; found 425.3392.

Carboxylic acid (1). The same procedure of conversion of **14** to the corresponding aldehyde **14a** was employed for the formation of **17** (81%) from **16**. A solution of sodium chlorite ($NaClO_2$, 64 mg, 80%, 0.566 mmol) and soduim dihydrogenphosphate (68 mg, 0.566 mmol) in H_2O (1.0 mL) was added to a solution of **17** (38 mg, 0.095 mmol) in *t*-BuOH (1 mL) and 2-methyl-2-butene (0.5 mL) at room temperature After 30 min, H_2O was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:3→1:1) to give **1** (27 mg, 68%) as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (2H, s), 1.25 (3H, s), 1.56 (6H, s), 1.59 (6H, s), 1.60–1.66 (2H, m), 1.94–2.07 (13H, m), 2.10–2.14 (1H, m), 2.28 (2H, t, $J=8.4$ Hz), 2.42 (2H, t, $J=8.0$ Hz), 2.70 (1H, dd, $J=6.1$, 6.1 Hz), 5.07–5.16 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.94, 15.96, 15.97, 16.01, 18.70, 24.84, 26.58, 26.61, 27.37, 28.02, 28.18, 32.89, 34.30, 36.26, 39.61, 39.68, 58.59, 64.30, 124.02, 124.29, 124.91, 125.27, 133.08, 133.91, 134.77, 135.25, 179.00; HRMS (MALDI-FTMS) calcd for $C_{27}H_{44}O_3$ ($M+Na^+$) 439.3188; found 439.3177.

Acetate (20). Alcohol **19** was prepared using a literature procedure.[20] The same procedure of conversion of **7** to **8** was used for the formation of **20** (100%) from **19** except using *t*-butyldiphenylsilyl chloride instead of *t*-butyldimethylsilyl chloride. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.67 (3H, s), 1.68–1.70 (2H, m), 2.04 (3H, s), 2.13 (2H, t, $J=7.6$ Hz), 3.63–3.67 (2H, m), 4.57 (2H, d, $J=7.3$ Hz), 5.32–5.35 (1H, m), 7.35–7.42 (6H, m), 7.65–7.68 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.35, 19.15, 21.00, 26.80, 30.44, 35.68, 61.30, 63.29, 118.25, 127.56, 129.50, 133.91, 135.50, 142.03, 171.04; HRMS (MALDI-FTMS) calcd for $C_{25}H_{34}O_3Si$ ($M+Na^+$) 433.2175; found 433.2167.

Alcohol (21). Acetate **20** (19.0 g, 46.3 mmol) was stirred with potassium carbonate (640 mg, 4.63 mmol) in MeOH at room temperature After 12 h, 1 N HCl was added to neutralized the mixture which was evaporated under reduced pressure. The residue was diluted with H_2O and then extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:4) to afford 14.1 g (83%) of **21** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.16 (1H, brs), 1.63 (3H, s), 1.65–1.70 (2H, m), 2.09 (2H, t, $J=8.2$ Hz), 3.64 (2H, t, $J=6.4$ Hz), 4.09–4.11 (2H, m), 5.35–5.39 (1H, m), 7.34–7.43 (6H, m), 7.64–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.20, 19.18, 26.83, 26.86, 30.56, 35.65, 59.31, 63.35, 123.36, 127.53, 127.56, 129.51, 133.96, 135.53, 139.49; HRMS (MALDI-FTMS) calcd for $C_{23}H_{32}O_2Si$ ($M+Na^+$) 391.2069; found 391.2069.

Sulfone (23). The same procedure of conversion of **5** to the corresponding iodide was used for the preparation of **22** (62%). Compound **22** (5.67 g, 11.86 mmol) was stirred with benzenesulfonic acid, sodium salt (4.5 g, 27.41 mmol) in DMF (50 mL) at 0 °C. After 30 min, the mixture was warmed to room temperature and H_2O (100 mL) was added. The mixture was extracted with

Et_2O and the combined extracts were dried over $MgSO_4$. Evaporation of solvent followed by column chromatography gave 5.36 g (92%) of **23** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.03(9H, s), 1.25 (3H, s), 1.51–1.58 (2H, m), 2.04 (2H, t, $J=7.6$ Hz), 3.58 (2H, t, $J=6.1$ Hz), 3.76 (2H, d, $J=7.9$ Hz), 5.13–5.17 (1H, m), 7.34–7.41 (6H, m), 7.44–7.48 (2H, m), 7.56–7.60 (1H, m), 7.62–7.64 (4H, m), 7.81–7.83 (2H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.04, 19.14, 26.78, 30.51, 35.85, 55.99, 63.19, 110.27, 127.57, 128.45, 128.88, 129.54, 133.46, 133.81, 135.47, 138.49, 146.23; HRMS (MALDI-FTMS) calcd for $C_{29}H_{36}O_3SSi$ ($M+Na^+$) 515.2052; found 515.2067.

Alcohol (25). *t*-BuLi (1.7 M in pentane) was added dropwise to a solution of ethyldiphenylsulfonium tetrafluoroborate in THF at −78 °C. The aldehyde **14a** (see above) in THF was added and the mixture was stirred for 30 min, before being quenched with satd NH_4Cl. The combined ethereal extracts of this mixture were dried over $MgSO_4$ and concentrated under reduced pressure. The remaining residue was purified by column chromatography to give **24**.

The silyl ether **24** was stirred with *n*-tetrabutylammonium fluoride in THF at room temperature After 12 h, H_2O was added and the mixture was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The obtained residue was purified by column chromatography to afford **25** (1:1 mixture of diastereomers, 21% over two steps). ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.24 (3H, s), 1.57 (9H, s), 1.58 (3H, s), 1.63–1.65 (4H, m), 1.94–2.06 (16H, m), 2.58–2.60 (0.5H, m), 2.71–2.72 (0.5H, m), 2.85–2.88 (0.5H, m), 2.99–3.02 (0.5H, m), 3.58–3.60 (2H, m), 5.08–5.15 (4H, m), ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.18, 15.86, 15.90, 15.97, 16.02, 17.67, 26.06, 26.57, 26.58, 28.12, 28.15, 28.16, 28.18, 29.66, 30.51, 30.70, 35.79, 35.98, 36.19, 39.57, 39.59, 39.69, 52.73, 54.73, 56.80, 59.54, 62.76, 124.10, 124.29, 124.33, 124.78, 124.84, 124.94, 133.85, 133.87, 134.73, 134.75, 135.20; HRMS (MALDI-FTMS) calcd for $C_{26}H_{44}O_2$ ($M+Na^+$) 411.3233; found 411.3240.

Carboxylic acid (2). The same procedure of conversion of **16** to **1** was used for the formation of **2** (1:1 mixture of diastereomers, 83%) from **25**. ^1H NMR (600 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.25 (3H, s), 1.57 (9H, s), 1.59 (3H, s), 1.60–1.66 (2H, m), 1.94–2.10 (14H, m), 2.26–2.29 (2H, m), 2.40–2.43 (2H, m), 2.60–2.61 (0.5H, m), 2.73–2.74 (0.5H, m), 2.87–2.90 (0.5H, m), 3.03–3.04 (0.5H, m), 5.07–5.16 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.16, 15.90, 15.94, 15.97, 16.01, 17.65, 26.02, 26.57, 26.60, 28.01, 28.18, 30.49, 32.85, 34.30, 35.81, 36.20, 39.59, 39.62, 39.68, 52.87, 54.86, 56.92, 59.66, 124.02, 124.28, 124.32, 124.87, 124.98, 125.28, 133.07, 133.82, 133.86, 134.76, 134.78, 135.25; HRMS (MALDI-FTMS) calcd for $C_{26}H_{42}O_3$ ($M+Na^+$) 425.3026; found 425.3033.

Dioxolane (27). Compound **18** (prepared using a literature procedure[20]) (1.300 g, 7.638 mmol) in toluene (125 mL) was treated with ethylene glycol (1.278 mL, 22.914 mmol) and *p*-toluene sulfonic acid (0.073 g, 0.382 mmol). The resulting solution was heated under reflux until water evolution ceased (3 h). The mixture was washed with satd Na_2CO_3 (50 mL), the aqueous layer was separated and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/hexane, 1:2) to give **27** (1.234 g, 70%) as a colorless oil.

Alcohol (28). Dioxolane **27** (0.756 g, 3.284 mmol) in MeOH (10 mL) was treated with satd K_2CO_3 (10 mL) at room temperature under vigorous stirring (1 h). The reaction mixture was diluted with ethyl acetate (100 mL), the aqueous layer separated and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexane, 2:1) to give **28** (0.545 g, 96%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (3H, s), 1.78 (2H, m), 2.14 (2H, m), 3.85 (2H, m), 3.97 (2H, m), 4.15 (2H, d, $J=6.8$ Hz), 4.86 (1H, t, $J=4.7$ Hz), 5.44 (1H, dt, $J=1.2/6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.94, 31.69, 33.34, 58.64, 64.52, 103.84, 123.59, 137.68; HRMS (MALDI-FTMS) calcd for $C_9H_{16}O_3$ ($M+Na^+$) 195.0992; found 195.0994.

Bromide (29). Compound **28** (1.249 g, 7.252 mmol) in CH_2Cl_2 (60 mL) under argon at −40 °C was consecutively treated with triethylamine (2.022 mL, 14.504 mmol) and mesyl chloride (10.878 mmol, 0.858 mL) and the resulting mixture was stirred at −40 °C for 1 h. LiBr (72.520 mmol, 6.298 g) in THF (120 mL) was added and the resulting mixture was stirred at room temperature for 1 h generating a white precipitate. Et_2O (100 mL) and satd NH_4Cl (5 mL) were added. The aqueous layer was separated and extracted with Et_2O (3×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give **29** (1.703 g) as a yellowish oil, that was introduced into the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (3H, s), 1.75 (2H, m), 2.16 (2H, m), 3.83 (2H, m), 3.94 (2H, m), 3.99 (2H, d, $J=8.2$ Hz), 4.83 (1H, t, $J=4.7$ Hz), 5.54 (1H, dt, $J=1.2/8.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.89, 29.38, 31.75, 33.52, 64.84, 103.80, 120.57, 142.70.

Sulfone (30). Compound **29** (1.703 g, 7.243 mmol) in DMF (36 mL) under argon at 0 °C was treated with $PhSO_2Na$ (1.784 mL, 10.865 mmol) in one portion and stirring was continued at 0 °C for 20 min. The reaction mixture was washed with water (15 mL) and the aqueous layer was extracted with Et_2O/hexane (1:1) (3×100 mL). followed by column chromatography (EtOAc/hexane, 1:3) gave **30** (1.719 g, 80%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.67 (2H, m), 2.10 (2H, m), 3.80 (2H, d, $J=7.9$ Hz), 3.85 (2H, m), 3.96 (2H, m), 4.81 (1H, t, $J=4.7$ Hz), 5.22 (1H, dt, $J=1.2/7.9$ Hz), 7.53 (2H, t, $J=7.4$ Hz), 7.64 (1H, t, $J=7.4$ Hz), 7.85 (2H, d, $J=7.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.09, 31.82, 33.71, 55.98, 64.87, 103.75, 110.63, 128.48, 128.95, 133.54, 138.49, 145.61; HRMS (MALDI-FTMS) calcd for $C_{15}H_{20}O_4S$ ($M+Na^+$) 319.0974; found 319.0973.

TMS-Enol ether (32). Diisopropylamine (3.222 mL, 22.998 mmol) in THF (22 mL) at −78 °C was treated with *n*-BuLi (9.637 mL, 2.5 M in hexane, 24.093 mmol) for 15 min, and stirring was continued for another 30 min at 0 °C. The mixture was cooled to −65 °C, **31** (commercially available) (3.000 g, 21.903 mmol) in THF (5 mL) was added dropwise and the mixture was stirred at this temperature for further 2 h. TMSCl (3.336 mL, 26.284 mmol) in THF (5 mL) was added dropwise and the resulting mixture was allowed to warm to room temperature over a 90-min period. After addition of pentane (200 mL) and cold satd Na_2CO_3 (50 mL), the aqueous layer was separated and extracted with pentane (3×100 mL). The combined organic layers were dried over $NaSO_4$, concentrated and purified by vacuum distillation (full oil pump vacuum, bp 42–52 °C) to give **32** (2.795 g, 84%) as a colorless oil.

Analytical data were in accord with the literature values.[23]

Dimethyl ester (33). TMS–enol ether **32** (2.781 g, 18.504 mmol) in CH_2Cl_2 (18.5 mL) under argon at 0 °C was treated dropwise with $TiCl_4$ (18.504 mL, 1 M in CH_2Cl_2, 18.504 mmol) under vigorous stirring. The resulting gray-green suspension was stirred for further 2 h. Quenching with H_2O (18.5 mL) was followed by extraction with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexane, 1:5) to give **33** (1.320 g, 63%) as white crystals.

Analytical data were in accord with the literature values.[23]

Diol (34). Compound **33** (27.693 mmol, 6.266 g) in CH_2Cl_2 (90 mL) under argon at −78 °C was treated dropwise with DIBAL (49.231 mmol, 73.846 mL, 1.5 M in toluene). The temperature was slowly raised to −10 °C over 2 h when the reaction was quenched with satd sodium potassium tartrate solution (18.5 mL). Stirring was continued for 2 h before the aqueous layer was separated and extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give **34** (4.593 g, 94%) as a colorless oil that was introduced into the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.66 (6H, s), 2.11 (4H, m), 4.00 (4H, s), 5.41 (2H, m), NOE ($CDCl_3$) δ 4.00: 1.66, 5.41; HRMS (MALDI-FTMS) calcd for $C_{10}H_{18}O_2$ ($M+Na^+$) 193. 1199; found 193.1206.

Mono silyl ether (35). To a suspension of sodium hydride (0.013 g, 3.270 mmol) in THF (5 mL) under argon was added dropwise **34** (0.559 g, 3.270 mmol) in THF (2 mL). After stirring for 45 min, TBS chloride (0.493 g, 3.270 mmol) was added in one portion and stirring was continued for 45 min The reaction mixture was poured into Et_2O (50 mL) and washed with 10% K_2CO_2 (20 mL). The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by column chromatography (Hex.→EA/MeOH, 10:1) to give monosilyl ether **35** (0.516 g, 55%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.89 (9H, s), 1.58 (3H, s), 1.64 (3H, s), 2.08 (4H, m), 3.96 (2H, s), 3.99 (2H, s), 5.38 (1H, sbr), 5.40 (1H, sbr), ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.34, 13.61, 15.16, 18.41, 25.89, 68.54, 68.80, 123.98, 125.78, 134.71, 135.00.

Bromide (36). Compound **35** (1.000 g, 3.515 mmol) was transformed to **36** with the same method used for the formation of bromide **29**. Bromide **36** (1.175 g) was obtained as a yellow oil that was introduced into the next step without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.90 (9H, s), 1.58 (3H, s), 1.74 (3H, s), 2.08 (4H, m), 3.95 (2H, s), 3.99 (2H, s), 5.36 (1H, sbr), 5.59 (1H, sbr); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.32, 13.47, 14.67, 18.41, 25.94, 26.95, 28.27, 41.83, 68.42, 123.38, 131.10, 132.20, 135.08; GC–MS: $[M-Br]^+ = 267$ (2%).

Compound 37. A solution of trimethysilylpropyne (1.496 mL, 10.103 mmol) in Et_2O (7 mL) under argon was cooled to −5 °C and TMEDA (1.677 mL, 11.114 mmol) was added in one portion. To this mixture a solution of *n*-buthyl lithium (6.947 mL, 1.6 M in hexane, 11.114 mmol) was added dropwise. and stirring was continued for 15 min. Now, **36** (1.170 g, 3.368 mmol) in Et_2O (3 mL) was added dropwise(!) and the resulting mixture was stirred at 0 °C overnight. Addition of satd NH_4Cl (5 mL) followed by extraction with Et_2O (3×10 mL) gave a combined organic phase that was dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:50) to give **37** (0.856 g, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.14 (9H, s), 0.91 (9H, s), 1.54 (3H, s), 1.60 (3H, s), 2.05 (4H, m), 2.19 (2H, t, $J=7.5$ Hz), 2.30 (2H, t, $J=7.5$ Hz), 4.00 (2H, s), 5.19 (1H, sbr), 5.39 (1H, sbr); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.27, 0.15, 13.43, 15.82, 18.41, 19.19, 25.96, 27.74, 27.93, 38.68, 68.65, 84.50, 107.35, 124.30, 125.42, 133.65, 134.53; GC–MS: $[M]^+ = 378$ (4%).

Monosubstituted alkine (38). Compound **37** (0.791 g, 2.077 mmol) was dissolved in MeOH (10 mL), potassium carbonate (0.432 g, 3.128 mmol) was added and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with water (6 mL) and extracted with hexane (3×25 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes 1:50) to give **38** (0.525 g, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.91 (9H, s), 1.59 (3H, s), 1.60 (3H, s), 1.94 (1H, sbr), 2.06 (4H, sbr), 2.20 (2H, t, $J=7.5$ Hz), 2.27 (2H, t, $J=7.5$ Hz), 4.00 (2H, s), 5.20 (1H, sbr), 5.39 (1H, sbr); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.28, 13.45, 15.80, 17.54, 18.41, 25.92, 27.65, 27.87, 38.42, 68.30, 68.61, 84.38, 124.23, 125.45, 133.43, 134.51; GC–MS: $[M]^+ = 306$ (1%).

Alkinol (39). Compound **38** (0.520 g, 1.696 mmol) in THF (2 mL) under argon at −60 °C was treated dropwise with *n*-butyllithium (0.780 mL, 2.5 M in hexane, 1.951 mmol), and the resulting mixture was stirred at −60 °C for 15 min before being allowed to warm to

−25 °C for 1.5 h. Upon renewed cooling to −60 °C *p*-formaldehyde (0.268 g, 8.481 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Addition of water (2 mL), followed by extration with Et_2O (3×10 mL) gave a combined organic phase that was dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:4) to give **39** (0.372 g, 65%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 1.57 (3H, s), 1.58 (3H, s), 2.04 (4H, sbr), 2.15 (2H, t, J = 7.5 Hz), 2.27 (2H, t, J = 7.5 Hz), 3.98 (2H, s), 4.19 (2H, s), 5.17 (1H, sbr), 5.38 (1H, sbr); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.37, 13.36, 15.74, 17.81, 18.30, 25.84, 27.57, 27.76, 38.48, 51.02, 68.51, 78.68, 85.81, 124.13, 125.30, 133.52, 134.37; HRMS (MALDI-FTMS) calcd for $C_{20}H_{34}O_2Si$ ($M + Na^+$) 359.2382; found 359.2380.

Allylic alcohol (40). A solution of *Red-Al*® (0.808 mL, 65 wt-% in toluene, 2.690 mmol) in toluene (8 mL) under argon at −78 °C was treated dropwise with a solution of **39** (0.283 g, 0.841 mmol) in toluene (4 mL). The resulting mixture was stirred at −78 °C for 1 h and was allowed to warm to room temperature overnight. Quenching was carried out with ethyl acetate (1 mL) and MeOH (1 mL). A satd sodium–potassium tartrate solution (5 mL) was added carefully and the resulting mixture stirred vigorously for 1 h. The aqueous layer was separated and extracted with diethyl ether (3×10 mL). The combined organic layers were dried over magnesium sulfate, concentrated and purified by column chromatography (EtOAc/hexanes, 1:5) to give **40** (0.198 g, 69%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.91 (9H, s), 1.58 (3H, s), 1.59 (3H, s), 2.04 (6H, m), 2.14 (2H, m), 4.00 (2H, sbr), 4.08 (2H, sbr), 5.15 (1H, sbr), 5.39 (1H, sbr), 5.66 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.31, 13.41, 15.97, 18.37, 25.88, 27.71, 27.83, 30.70, 39.13, 63.63, 68.58, 124.28, 124.50, 128.94, 132.86, 134.38, 134.56.

Bromide (41). Compound **40** (0.550 g, 1.624 mmol) was transformed to **41** with the same method used for the formation of bromide **29**. Bromide **41** (0.616 g, 94%) was obtained as a yellow oil that was introduced into the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.91 (9H, s), 1.59 (6H, s), 2.05 (6H, sbr), 2.16 (2H, m), 3.94 (2H, d, J = 7.3 Hz), 4.01 (2H, s), 5.14 (1H, sbr), 5.39 (1H, sbr), 5.72 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.31, 13.42, 15.96, 18.37, 25.91, 27.70, 27.84, 30.53, 33.45, 38.73, 68.57, 124.25, 124.78, 126.30, 134.14, 134.43, 136.15.

Allylic sulfone (42). A solution of sulfone **30** (0.646 g, 2.179 mmol) in THF (8 mL) under argon at −78 °C was treated dropwise with *n*-BuLi (1.318 mL, 1.6 M in hexane, 2.109 mmol) and stirring was continued for 1 h. Now, bromide **41** (0.244 g, 0.703 mmol) in THF (2 mL) was added dropwise and the mixture was stirred at −78 °C for 10 h before being slowly warmed to room temperature. Addition of sat. NH_4Cl (10 mL) was followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:3) to give **42** (0.361 g, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.91 (9H, s), 1.21 (3H, s), 1.26 (2H, m), 1.56 (6H, s), 1.64 (2H, m), 1.95 (2H, m), 2.00–2.10 (8H, m), 2.32 (1H, m), 2.84 (1H, m), 3.74 (1H, dt, J = 3.1/10.4 Hz), 3.85 (2H, m), 3.95 (2H, m), 4.00 (2H, s), 4.79 (1H, t, J = 4.5 Hz), 5.00 (1H, d, J = 10.4Hz), 5.11 (1H, t, J = 7.6 Hz), 5.23 (1H, dt, J = 6.8/7.5 Hz), 5.38 (1H, t, J = 6.6 Hz), 5.49 (1H, dt, J = 6.8/7.5 Hz), 7.51 (2H, t, J = 7.6 Hz), 7.61 (1H, t, J = 7.6 Hz), 7.82 (2H, d, J = 7.6 Hz); HRMS (MALDI-FTMS) calcd for $C_{35}H_{56}O_5SSi$ ($M + Na^+$) 639.3510; found 639.3511.

Key intermediate (43). A solution of $Pd(OAc)_2$ (0.022 g, 0.098 mmol) and dppp (0.040 g, 0.098 mmol) in degassed THF (2 mL) under argon was strirred at room temperature for 30 min during which a fine solid precipitates. This mixture was cooled to 0 °C and **42** (0.605 g, 0.981 mmol) in THF (5 mL) was added dropwise. After stirring for 5 min, a solution of super hydride™ (1.962 mL, 1 M in THF, 1.962 mmol) was added *very slowly* (ca. 2 h). The reaction progress was followed by TLC and stopped immediately upon completion to prevent significant cleavage of the allylic TBS–ether. Best results were obtained when the whole amount of super hydride™ was kept under argon in a dry scintillation vial, sealed by a septum. Little portions were taken out, using a fresh plastic syringe with a new disposable needle (since the super hydride™ solution seemed to be corrosive). It was made sure to empty the volume of the needle after each injection. The resulting mixture was stirred at 0 °C for 2 h before being warmed to room temperature (1 h). Quenching was carried out with sat. NH_4Cl (10 mL). The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:5) to give **43** (0.389 g, 83%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.91 (9H, s), 1.58 (3H, s), 1.59 (3H, s), 1.60 (3H, s), 1.75 (2H, m), 1.97–2.11 (14H, m), 3.84 (2H, m), 3.97 (2H, m), 4.00 (2H, s), 4.85 (1H, t, J = 4.8 Hz), 5.13 (1H, sbr), 5.16 (1H, sbr), 5.39 (2H, sbr); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.28, 13.43, 16.04, 18.41, 25.95, 27.82, 28.08, 30.28, 31.24, 32.43, 32.72, 33.87, 39.74, 64.82, 68.67, 104.34, 124.17, 124.28, 124.45, 129.86, 130.21, 134.27, 134.39, 135.01; HRMS (MALDI-FTMS) calcd for $C_{29}H_{52}O_3Si$ ($M + Na^+$) 499.3578; found 499.3580.

Alcohol (44). Silicagel (1.632 g, 2 g/mmol) was added to a solution of compound **43** (0.389 g, 0.816 mmol) in THF (16 mL) under argon and the mixture was cooled to −50 °C. TBAF (1.036 mL, 1 M in THF, 1.036 mmol) was added dropwise and the resulting mixture was stirred for 1 h, before being warmed to room temperature over 30 min and then heated to 50 °C for 2 h. Upon addition of satd NaCl (20 mL) at room temperature, the aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:5) to give **44** (0.264 g, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 1.75

(2H, m), 1.97–2.13 (14H, m), 3.85 (2H, m), 3.97 (2H, m), 4.00 (2H, s), 4.85 (1H, t, $J=4.8$ Hz), 5.13 (1H, sbr), 5.16 (1H, sbr), 5.40 (2H, sbr) 5.42 (1H, sbr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.69, 16.07, 27.83, 27.92, 28.09, 31.23, 32.47, 32.72, 33.88, 39.73, 64.85, 69.03, 104.38, 123.99, 124.28, 126.13, 129.94, 130.16, 134.32, 134.86, 135.27; HRMS (MALDI-FTMS) calcd for $C_{23}H_{38}O_3$ ($M+Na^+$) 385.2713; found 385.2701.

Tricarboxylic ester (45). Alcohol **44** (0.025 g, 0.069 mmol) in Et_2O (1 mL) under argon was treated with triphenyl phosphine (0.054 g, 0.206 mmol) and triethyl methanetricarboxylate (TEMT) (0.034 g, 0.166 mmol) and cooled to 0 °C. A solution of DEAD (0.032 mL, 0.6 M in Et_2O, 0.206 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. After addition of 5% $NaHCO_3$ (3 mL) and extraction with Et_2O (3×10 mL), the combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes 1:5) to give **45** (0.033 g, 83%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (9H, t, $J=7.1$), 1.56 (3H, s), 1.57 (3H, s), 1.59 (3H, s), 1.75 (2H, m), 1.95–2.07 (14H, m), 2.96 (2H, s), 3.84 (2H, m), 3.96 (2H, m), 4.21 (6H, q, $J=7.1$ Hz), 4.84 (1H, t, $J=4.8$ Hz), 5.10 (1H, sbr), 5.16 (1H, sbr), 5.23 (1H, sbr), 5.38 (2H, sbr); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.86, 16.01, 16.45, 27.81, 28.08, 28.33, 31.24, 32.42, 32.72, 33.87, 39.71, 43.07, 61.87, 62.41, 64.84, 104.33, 123.99, 124.27, 129.89, 129.92, 130.16, 130.19, 134.27, 135.15, 166.50; HRMS (MALDI-FTMS) calcd for $C_{33}H_{52}O_8$ ($M+Na^+$) 599.3554; found 599.3558.

Monocarboxylic ester (46). Lithium chloride (0.054 g, 1.284 mmol) in water (0.007 g, 0.428 mmol) was added to a solution of compound **23** (0.247 g, 0.428 mmol) in DMSO (0.5 mL) in a pressure bottle. The sealed bottle was heated to 189 °C for 9 h. After cooling, hexane (1 mL) was added and the aqueous layer extracted with hexane (3×50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:5) to give **46** (0.118 g, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (3H, t, $J=7.1$), 1.56 (3H, s), 1.58 (3H, s), 1.59 (3H, s), 1.75 (2H, m), 1.95–2.07 (14H, m), 2.29 (2H, t, $J=7.2$), 2.39 (2H, t, $J=7.2$), 3.85 (2H, m), 3.96 (2H, m), 4.11 (2H, q, $J=7.1$ Hz), 4.85 (1H, t, $J=4.6$ Hz), 5.11 (1H, sbr), 5.16 (2H, sbr), 5.40 (2H, sbr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.24, 15.93, 16.03, 16.06, 28.04, 28.08, 28.20, 31.26, 32.43, 32.73, 33.25, 33.87, 34.69, 39.74, 60.22, 64.84, 104.34, 124.12, 124.27, 125.09, 129.89, 130.19, 133.42, 134.28, 135.04, 173.55; HRMS (MALDI-FTMS) calcd for $C_{27}H_{44}O_4$ ($M+Na^+$) 455.3132; found 455.3132.

Aldehyde (47). Monocarboxylic ester **46** (0.008 g, 0.002 mmol) was dissolved in acetone (1 mL) and one droplet of water was added. To this solution *p*-toluenesulfonic acid (0.001 g) was added and the mixture was heated to 50 °C for 5 h. After cooling to room temperature the mixture was diluted with Et_2O (10 mL) and washed with satd $NaHCO_3$ (3 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes 1:5) to give **47** (0.006 g, 77%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24 (3H, t, $J=7.1$), 1.58 (3H, s), 1.60 (6H, s), 1.95–2.07 (12H, m), 2.27–2.35 (4H, m), 2.36–2.41 (2H, m), 2.48–2.52 (2H, m), 4.11 (2H, q, $J=7.1$ Hz), 5.11 (1H, sbr), 5.16 (1H, sbr), 5.17 (1H, sbr), 5.39 (2H, sbr), 9.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.23, 15.91, 16.01, 16.10, 28.02, 28.19, 28.20, 31.23, 31.84, 32.59, 33.26, 34.69, 39.71, 42.14, 60.18, 124.16, 125.08, 125.20, 129.65, 130.37, 133.07, 133.42, 135.00, 173.47, 202.61; HRMS (MALDI-FTMS) calcd for $C_{25}H_{40}O_3$ ($M+Na^+$) 411.2869; found 411.2868.

Epoxide (48). $[Ph_2(i\text{-prop})S]^+BF_4^-$ (0.115 g, 0.386 mmol) in THF (1 mL) at −78 °C was treated dropwise with *t*-BuLi (0.227 mL, 1.7 M in pentane, 0.386 mmol) and stirring was continued for 1 h. Aldehyde **47** (0.030 g, 0.077 mmol) in THF (0.5 mL) was added and the resulting solution stirred at −78 °C for further 30 min The reaction was quenched with brine (3 mL), the aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes 1:5) to give **26** (0.020 g, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (3H, t, $J=7.1$), 1.26 (3H, s), 1.30 (3H, s), 1.60 (3H, s), 1.66 (6H, s), 1.95–2.21 (16H, m), 2.29 (2H, m), 2.39 (2H, m), 2.70 (1H, t, $J=6.2$), 4.12 (2H, q, $J=7.1$ Hz), 5.12 (1H, sbr), 5.16 (1H, sbr), 5.17 (1H, sbr), 5.40 (2H, sbr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.24, 15.91, 15.96, 16.02, 18.73, 24.89, 26.39, 27.42, 28.05, 28.11, 28.20, 29.68, 30.29, 31.25, 32.73, 33.08, 34.69, 39.74, 43.44, 58.33, 60.20, 64.19, 124.14, 124.68, 125.08, 129.84, 130.25, 133.42, 134.21, 135.01, 173.53; HRMS (MALDI-FTMS) calcd for $C_{28}H_{46}O_3$ ($M+Na^+$) 453.3339; found 453.3344.

Carboxylic acid (3). Ethyl ester **48** (0.016 g, 0.037 mmol) was dissolved in MeOH (1 mL) and five droplets of a 1 M NaOH were added. The mixture was stirred at room temperature overnight, diluted with Et_2O (10 mL) and washed with brine (3 mL). The aqueous layer was separated, neutralized with three droplets of citric acid and extracted with Et_2O (10 mL each). The combined organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc/hexanes, 1:5) to give **3** (0.015 g, 99%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.31 (3H, s), 1.58 (3H, s), 1.56–1.72 (2H, m), 1.61 (3H, s), 1.62 (3H, s), 1.95–2.12 (13H, m), 2.15 (1H, m), 2.31 (2H, t, $J=7.6$ Hz), 2.45 (2H, t, $J=7.6$ Hz), 2.73 (1H, t, $J=6.2$), 5.11 (1H, sbr), 5.17 (1H, sbr), 5.18 (1H, sbr), 5.40 (2H, sbr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.96, 16.03, 18.73, 24.85, 27.37, 27.98, 28.12, 28.16, 31.19, 32.60, 32.73, 34.37, 36.30, 39.71, 58.65, 64.32, 124.18, 124.78, 125.30, 129.89, 130.26, 133.13, 134.16, 135.03, 177.98; HRMS (MALDI-FTMS) calcd for $C_{26}H_{42}O_3$ ($M+Na^+$) 425.3026; found 425.3008.

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