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Ring-closing metathesis and palladium-catalyzed formate reduction to 3-methyleneoxepanes. Formal synthesis of (−)-zoapatanol

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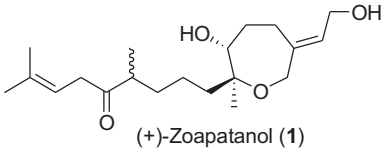
ABSTRACT

A sequence of ring-closing metathesis and palladium-catalyzed formate reduction was developed for preparing *O*-heterocycles with an exocyclic olefin and applied to the asymmetric synthesis of zoapatanol. The key vicinal stereocenters in zoapatanol were constructed from the L-malic acid-derived lactone by successive chelation-controlled addition of alkyl groups. The O-allylations to prepare the dienes for RCM were achieved with the tertiary alcohols bearing internal olefins. The ring opening of oxepane, a new reaction pathway for the Pd-formate reduction, is also reported.

1. Introduction

Zoapatanol (**1**), a novel diterpenoid oxepane (Fig. 1) was isolated from the leaves of the Mexican zoapatle plant *Montanoa tomentosa*[1] and has received attention owing to its potential as an antifertility agent[2] and its challenging structure. Although several groups have reported total syntheses of zoapatanol,[3,4] only two have achieved an asymmetric synthesis, utilizing Sharpless asymmetric epoxidation and dihydroxylation to construct the vicinal stereocenters.[4,5] Other asymmetric approaches that were not pursued to completion have also been described.[6]



(+)-Zoapatanol (**1**)

Fig. 1. Zoapatanol.

In addition to the stereochemical issue, the formation of an oxepane bearing an exocyclic olefin is another concern. However, ring-closing metathesis (RCM) is an ideal protocol for preparing cyclic compounds, owing to the excellent tolerance of functional groups to it and its broad applicability to different ring sizes.[7,8] Indeed, RCM has been applied to construct the oxepane core of zopatanol by Boom's and Cossy's groups.[4c,6d] Unfortunately, further modifications on the endocyclic olefin that resulted in order to obtain the desired exocyclic olefin were unsuccessful.[4c] We felt that this key endocyclic to exocyclic transformation could be solved by the palladium-catalyzed formate reduction of allylic acetates as recently developed by our group for affording *N*-heterocycles.[9] Herein we report our studies involving combination of RCM and palladium-catalyzed formate reduction to generate *O*-heterocycles containing an exocyclic olefin function. A new asymmetric approach to generate the vicinal stereocenters was also developed in this formal synthesis.

2. Results and discussion

Our retrosynthetic analysis of zoapatanol is shown in Scheme 1. We planned to form the tetrahydrooxepin by RCM, followed by Pd-catalyzed formate reduction to afford the exocyclic olefin. Allylation of a tertiary alcohol would produce the diene required for RCM, and the key stereochemistry would be constructed by successive chelation-controlled addition of alkyl groups, starting with the malic acid-derived lactone.

Dihydropyan **5a** and tetrahydrooxepin **5b** were prepared as the model substrates since regioselective Pd-catalyzed formate reduction in *O*-heterocycles to give an exocyclic olefin had not been studied before. The tertiary alcohols **2**[11] were chosen to mimic the ether linkage in zoapatanol and were converted to the allylic alcohols **4** by Williamson ether synthesis with allyl chloride **3**[12]

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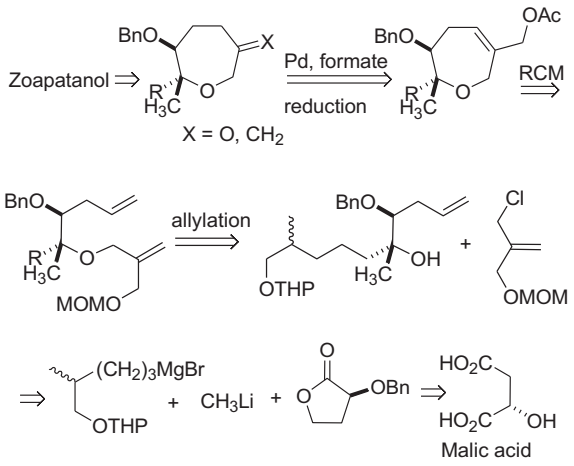
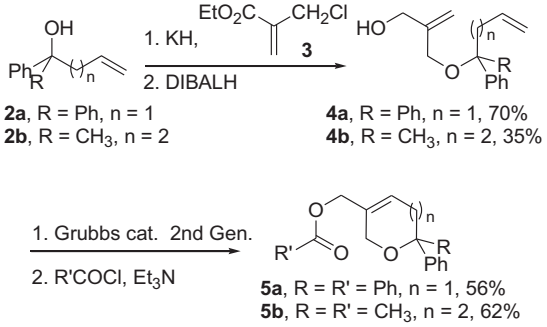


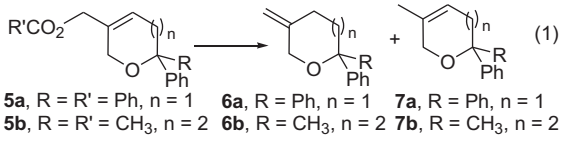
Scheme 1. Retrosynthetic analysis of zoapatanol.

followed by reduction with DIBALH. Ring-closing metathesis and acylation gave the allyl esters **5** (Scheme 2).



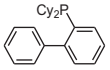
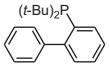
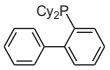
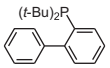
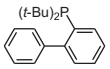
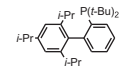
Scheme 2. Preparation of **5**.

Selected results from screening phosphine ligands for the Pd-catalyzed formate reductions of **5** [Eq. 1] are summarized in Table 1. Here, the general reaction parameters, such as the solvent, reagent/catalyst equivalents, reaction temperatures, and time, were modeled after our previous studies with *N*-heterocycles.[9a] Monodentate phosphines such as P(*n*-Bu)$_3$ and PCy$_3$, which have often been applied to this reaction with linear substrates,[13] gave only moderate regioselectivities (entries 1 and 2). The reaction became very sluggish when the bulky P(*t*-Bu)$_3$ was used, in spite of the exclusive formation of the *exo*-product (entry 3). We were surprised to find that triphenylphosphine was effective for preparing **6a** (entry 4), but gave only modest selectivity with the seven-membered substrate **5b** (entry 7). Biphenyldialkylphosphines[14] consistently gave good to excellent selectivities in favor of the *exo*-products **6** (entries 5, 6 and 10, 11). Further increase in the steric demands of the Buchwald-type phosphine ligands did not give better results (entry 12). Thus, (2-biphenyl)di-*tert*-butylphosphine was the choice of the ligand in our ultimate synthesis of zoapatanol. In addition to the use of allylpalladium chloride dimer as the source of palladium, Pd$_2$(dba)$_3$ can also be applied with convenience in stoichiometric amounts.



(1)

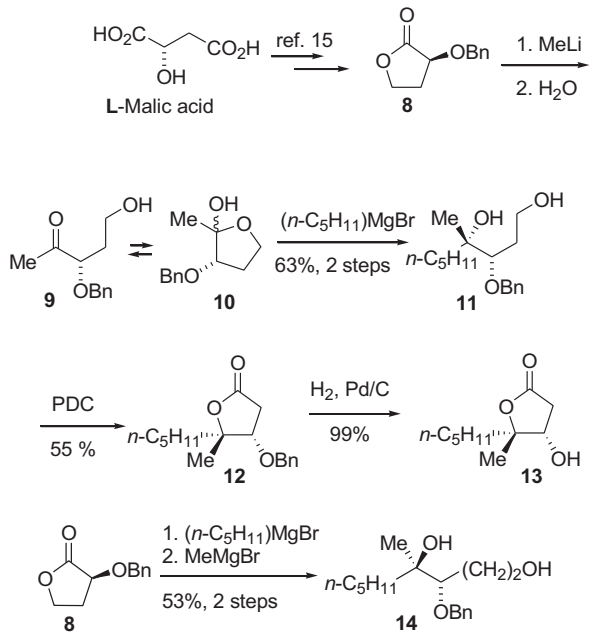
Table 1
Palladium-catalyzed formate reduction of **5**

Entry	Substrate	PR$_3$	Condition[a]	Conv. (%)	Ratio[b] (**6**/**7**)[c]
1	**5a**	P(*n*-Bu)$_3$	A	99	87/13
2	**5a**	PCy$_3$	A	80	58/42
3	**5a**	P(*t*-Bu)$_3$	A	12	100/0
4	**5a**	PPh$_3$	A	>99	99.7/0.3
5	**5a**		A	99	94/6
6	**5a**		A	99	84/16
7	**5b**	PPh$_3$	B	>99	77/23
8	**5b**	P(*o*-Tol)$_3$	B	81	52/48
9	**5b**		B	56	50/50
10	**5b**		B[c]	67	100/0
11	**5b**		B[d]	>99	95/5
12	**5b**		B	43	37/63

[a] The reactions were performed at 25 °C, 16 h, with Pd (10 mol %), PR$_3$ (20 mol %), formic acid (5 equiv), and triethylamine (6 equiv) in DMF; A: allylpalladium chloride dimer was used; B: Pd$_2$(dba)$_3$.
[b] Ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.
[c] 40 °C, 16 h.
[d] 40 °C, 24 h.

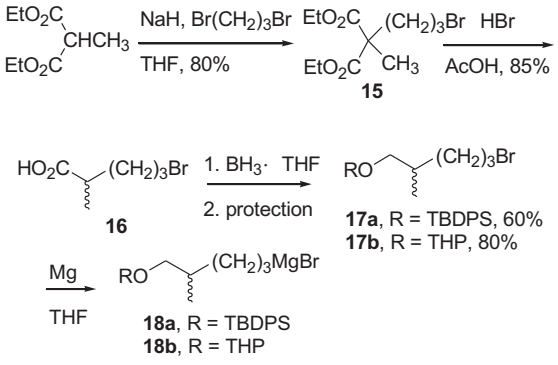
After defining the method for generating the exocyclic olefin, our synthesis of zoapatanol started from the lactone **8**, derived from inexpensive L-malic acid according to literature procedures.[15] The stereochemical issue associated with addition of alkyl groups, starting with **8**, to give tertiary alcohols such as **11** and **14** (Scheme 3) had not been previously addressed, although the diastereoselective formation of the corresponding secondary alcohol by the DIBALH reduction and Grignard alkylation of **8** is known.[16] Methyllithium and *n*-pentylmagnesium bromide rather than the racemic nucleophiles **18** required for the synthesis of zoapatanol but complicated NMR analysis of the product (vide infra), were selected to study the stereochemistry of the acyl substitution and alkyl addition. Thus, reaction of **8** with methyllithium generated the equilibrated mixture of *g*-hydroxyl ketone **9** and hemiacetal **10**.[17] Subsequent addition of *n*-pentyl magnesium bromide gave the diol **11** with excellent diastereoselectivity (>20:1).[18] The stereochemical outcome was initially assumed as (3*S*,4*S*) according to the Cram chelation model.[19] This rationale was later confirmed by converting **11** to the known *g*-butyrolactones **13**.[20] Alternating the order of alkylation gave the (3*S*,4*R*)-diastereomer **14** (Scheme 3), thereby establishing the stereochemistry associated with this synthetic approach. We also observed that the addition reaction was only effective with methylmagnesium bromide, not methyllithium.

The Grignard reagent **18** required for incorporating the carbonic side chain was prepared from the corresponding alkylbromide **17**, which was derived from diethyl methylmalonate after a series of transformations, including alkylation, decarboxylation, reduction, and protection (Scheme 4). Both diastereomeric diols **19** and **20**, the

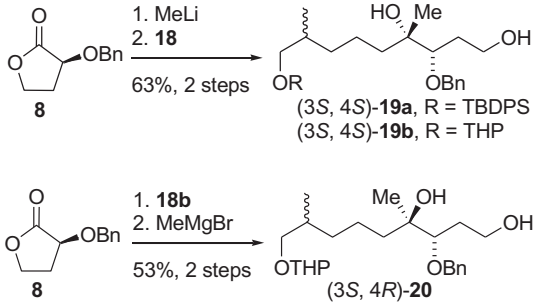


Scheme 3. Chelation-controlled alkylations.

precursors to zoapatanol, were prepared after alternating the sequence of the alkylations (Scheme 5).

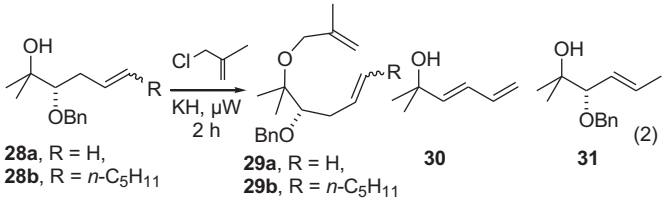


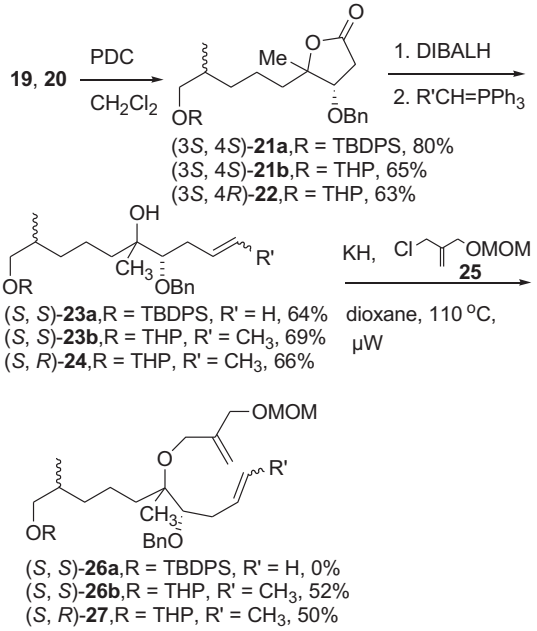
Scheme 4. Preparation of **18**.



Scheme 5. Synthesis of diols **19** and **20**.

Conversion of the diols **19** and **20** to the corresponding dienes for RCM is outlined in Scheme 6. The terminal alcohols **19** and **20** were oxidized with pyridinium dichromate to give lactones **21** and **22**.[21] Subsequent DIBALH reduction and Wittig olefination provided alkenes **23** and **24**. However, the ensuing allylation was difficult, as our initial attempts with **23a** did not yield any of the desired product. Although the previous allylation using the model, tertiary alcohols **2** went smoothly (Scheme 2), the corresponding reactions of **23a** with various allyl halides were unsuccessful. It seems clear that the additional benzyloxyl group of **23** hinders the allylation. We therefore resorted to analyzing the allylation with the simplified tertiary alcohols **28a** and **b** and 3-chloro-2-methyl-1-propene [Eq. 2, Table 2].[22] Indeed, higher reaction temperatures, assisted by microwave heating, were necessary to facilitate the allylation of **28**, but two by-products, **30** and **31**, derived from the elimination of the benzyloxyl group and the migration of the olefin, respectively, were also observed under such harsh conditions. Since these unwanted pathways were all related with the olefin moiety and became dominant with the terminal olefin **28a** (Table 2, entries 1–4), we were glad to find that having an internal olefin, as with **28b**, circumvented these problems, and the corresponding diene **29b** could be prepared (entries 6 and 7).





Scheme 6. Syntheses of the dienes **26** and **27**.

Consequently, internal olefins **23b** and **24** were prepared and their allylations with **25** went smoothly as expected to give the dienes **26b** and **27**. We found that the THP protecting group was more stable than the TBDPS group for the allylation.

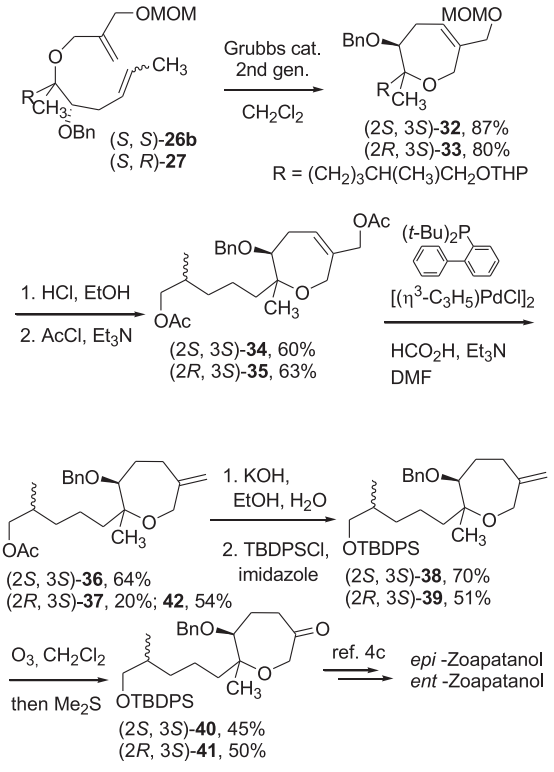
Ring-closing metatheses between the 1,1- and 1,2-disubstituted olefins in **26b** and **27** were performed at elevated temperatures (110 °C, 20 min), and the oxepanes **32** and **33** were produced in good yields. The MOM and THP protecting groups were replaced

Table 2
Allylation of tertiary alcohols **28**

Entry	Reactant	Solvent	Temp (°C)	Product[a]
1	**28a**	DMF	120	**29a**(40%), **31**(60%)
2	**28a**	HMPA	120	**30**
3	**28a**	Toluene	120	**31**
4	**28a**	Dioxane	120	**29a** (28%), **31** (59%)
5	**28b**	THF	120	**29b** (20%)
6	**28b**	Dioxane	120	**29b** (27%)
7	**28b**	Dioxane	110	**29b** (71%)[b]

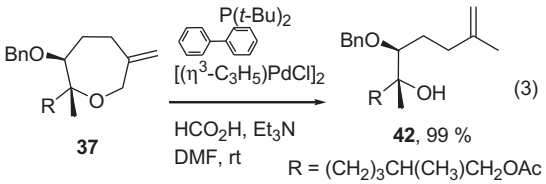
[a] Ratios were determined by ^{1}H NMR of crude reaction mixtures.
[b] 8 h.

with acetyl groups to give **34** and **35**, the substrates for the endocyclic to exocyclic conversions. Performing Pd-catalyzed formate reduction of **34** and **35** using (2-biphenyl)di-*tert*-butylphosphine gave the desired 3-methyleneoxepanes **36** and **37**. Then the key intermediate **41** in Cossy's synthesis of zoapatanol[4c] was produced upon changing the hydroxyl-protecting group to TBDPS and subsequent ozonolysis. The spectroscopic data of our synthetic **41** were consistent with the reported values, except for the opposite direction of optical rotation (Scheme 7).[4b,c]



Scheme 7. Formal syntheses of zoapatanols.

With respect to the low yield of **37** as compared to that of **36** was found to be the result of the formation of the ring-opened compound **42** in 54% yield. The origin of **42** by over-reduction of **37** was later substantiated by quantitatively transforming **37** to **42** under the reaction conditions used for the formate reduction [Eq. 3]. It is interesting to note that the reaction of diastereomer **34** was free of this over-reduced product, suggesting that compound **37** is more susceptible to the ring opening of the cyclic, allylic ether. Although the ring opening of strained, vinyl epoxides by the Pd-catalyzed reduction is known,[23] the ring opening of other allylic cyclic ethers under such conditions has not been reported. Theoretical calculations showed that the ground state conformers of **36** and **37** were very similar; however, **36** was slightly more stable by 0.80 kcal/mol in Gibbs free energy (25 °C).[24]



3. Conclusion

We have demonstrated that the combination of ring-closing metathesis and palladium-catalyzed formate reduction was useful for preparing zoapatanol, an *O*-heterocycle with an exocyclic olefin moiety. In our synthesis, the vicinal stereocenters of zoapatanol were derived from malic acid, and both epimers were prepared with excellent stereocontrol. Since both L- and D-malic acids are commercially available, this synthesis should allow the preparation of all the stereoisomers of zoapatanol. The allylation of the sterically hindered tertiary alcohols was achieved by modifying the olefin from terminal to internal. Thus, the chemically inert methyl group can be considered as a protecting group for the labile terminal olefin since the ring-closing metathesis of the internal olefin was successful and removed the additional methyl group. We believe that this sequence of RCM and Pd-catalyzed formate reduction can also be applied to prepare other heterocycles, where exocyclic olefins are in need.

4. Experimental section

4.1. General

4.1.1. Palladium-catalyzed formate reduction. Triethylamine (95 μL, 0.69 mmol) and formic acid (25 μL, 0.69 mmol) were added to a solution of $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol) and (2-biphenyl)di-*tert*-butylphosphine (6.86 mg, 0.023 mmol) in DMF (1.5 mL) under an atmosphere of nitrogen. The solution was stirred at rt for 5 min. Acetate **5b** (30 mg, 0.12 mmol) in DMF (400 μL) was added to the solution of the palladium complex. After being stirred at 40 °C for 24 h, the reaction mixture was diluted withCH_2Cl_2 (10 mL), washed with water (2 mL×2) and saturated $NaCl_{(aq)}$ (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **6b** to **7b** and further purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:9; R_f 0.80) to give **6b** (20 mg, 0.10 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.21 (m, 5H), 4.79 (s, 2H), 4.05–3.83 (dd, J=13.5 Hz, 1H), 2.50–2.44 (m, 1H), 2.42–2.11 (m, 3H), 1.73–1.69 (m, 2H), 1.55 (s, 2H), 1.37 (s, 3H), 1.23–1.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 148.2, 128.2, 126.4, 125.3, 111.9, 79.9, 68.4, 38.8, 36.1, 30.6, 29.7, 21.9; HRMS (HR-API) calcd for [M+Na] $C_{14}H_{19}O$: 203.1437, found 203.1436.

*4.1.2. Compound **20**.* Grignard reagent **18b** (0.28 M in THF, 16 mL, 4.48 mmol) was added to a solution of **8** (760 mg, 3.9 mmol) in THF (30 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was added to saturated $NH_4Cl_{(aq)}$ (10 mL) and extracted with diethyl ether (2×20 mL). The combined organic layers were washed with $NaCl_{(aq)}$ (20 mL), dried (Na_2SO_4), and concentrated. The crude ketone (2.1 g) was redissolved in diethyl ether (35 mL), and methylmagnesium bromide (3.0 M in diethyl ether, 7 mL, 21.1 mmol) was added to the solution dropwise at 0 °C. The

reaction mixture was stirred for 14 h, having warmed to rt during this period. Saturated $NH_4Cl_{(aq)}$ was added, and the mixtures were extracted with diethyl ether (2×20 mL). The organic layers were combined, washed with saturated $NaCl_{(aq)}$, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:1; R_f 0.42) to give **20** (830 mg, 2.1 mmol, 53%, two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 4.64 (d, J=11.2 Hz, 1H), 4.54–4.51 (m, 1H), 4.53 (d, J=11.2 Hz, 1H), 3.87–3.73 (m, 2H), 3.69–3.52 (m, 1.5H), 3.52–3.36 (m, 2.5H), 3.24–3.06 (m, 1H), 2.70 (br, 2H), 1.92–1.73 (m, 3H), 1.73–1.60 (m, 2H), 1.60–1.42 (m, 6H), 1.42–1.25 (m, 3H), 1.18 (s, 3H), 1.14–1.02 (m, 1H), 0.89 (2d, J=5.3 Hz, 2×1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 99.1, 99.0, 98.9, 98.8, 83.2, 74.9, 73.7, 73.1, 73.0, 72.9, 62.2, 62.1, 59.3, 38.1, 34.3, 33.4, 33.3, 32.2, 30.7, 25.5, 23.7, 20.7, 20.6, 19.5, 17.2, 17.1. IR (neat) 3413, 2941, 2874, 1640, 1453, 1375, 1027, 737 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{38}O_6Na$: 417.2617, found: 417.2623; $[\alpha]_D^{20}$ +1.92 (*c* 1.3, $CHCl_3$).

*4.1.3. Compound (3S,4R)-**22**.* A suspension of diol **20** (1.1 g, 2.7 mmol), molecular sieves (4 Å, 10 g) and pyridinium dichromate (4.3 g, 11.4 mmol) in dichloromethane (50 mL) was stirred at rt for 14 h. The reaction mixture was diluted with ethyl acetate (50 mL), filtered through a pad of Celite 545, and concentrated. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:3; R_f 0.42) to give **22** (0.68 g, 1.7 mmol, 63%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H), 4.55 (d, J=11.9 Hz, 1H), 4.55–4.50 (m, 1H), 4.44 (d, J=11.9 Hz, 1H), 3.94–3.91 (m, 1H), 3.85–3.78 (m, 1H), 3.55–3.44 (m, 2H), 3.18–3.10 (m, 1H), 2.76 (dd, J=17.7 Hz, 7.0 Hz, 1H), 2.58 (dd, J=17.7 Hz, 5.5 Hz, 1H), 1.82–1.63 (m, 4H), 1.60–1.45 (m, 7H), 1.43–1.27 (m, 1H), 1.38 (s, 3H), 1.12–1.04 (m, 1H), 0.88 (2d, J=6.9 Hz, 2×1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 137.2, 128.4, 127.9, 127.6, 127.4, 99.0, 98.9, 98.8, 89.0, 88.9, 78.7, 78.6, 72.9, 72.8, 72.7, 72.0, 62.2, 62.1, 40.1, 40.0, 35.2, 33.8, 33.2, 30.6, 25.4, 20.9, 19.6, 19.5, 19.3, 19.2, 17.0, 16.9, 16.8; IR (neat) 2941, 2869, 1774, 1727, 1457, 1380, 1271, 1121, 1027, 975, 742, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{34}O_5Na$ 413.2304, found 413.2296. $[\alpha]_D^{20}$ +29.7 (*c* 1.15, $CHCl_3$).

*4.1.4. Compound (S,R)-**24**.* Diisobutylaluminium hydride (1.0 M in cyclohexane, 0.4 mL, 0.4 mmol) was added to a solution of **22** (100 mg, 0.26 mmol) in dichloromethane (4 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, quenched with saturated $NH_4Cl_{(aq)}$ (0.5 mL), diluted with diethylether (10 mL), warmed to rt, and filtered. The filtrate was washed with water (5 mL), saturated $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), and concentrated to give the crude lactol (91 mg). A solution of ethylidene(triphenyl) phosphorane was prepared from ethyltriphenylphosphonium bromide (407 mg, 1.1 mmol) and *n*-butyllithium (1.6 M, 0.6 mL, 0.96 mmol) in THF (4 mL) at 0 °C. The ylide was added to the solution of the lactol in THF (4 mL) at −78 °C. After the addition, the reaction mixture was warmed to rt and heated at reflux for 2 h, quenched with saturated $NH_4Cl_{(aq)}$ (5 mL), and extracted with diethylether (2×20 mL). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:4; R_f 0.40) to give **24** (69 mg, 0.17 mmol, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 5.62–5.45 (m, 2H), 4.72 (d, J=11.1 Hz, 1H), 4.56–4.51 (m, 1H), 4.48 (d, J=11.1 Hz, 1H), 3.88–3.77 (m, 1H), 3.62–3.41 (m, 2H), 3.32–3.26 (m, 1H), 3.26–3.08 (m, 1H), 2.39 (m, 2H), 2.20–2.11 (m, 1H), 1.88–1.70 (m, 2H), 1.70–1.61 (m, 1H), 1.64 (d, J=5.4 Hz, 3H), 1.60–1.31 (m, 9H), 1.16 (s, 3H), 1.13–1.02 (m, 1H), 0.92–0.88 (2d, J=6.4 Hz, 2×1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.6, 128.2, 127.7, 127.6, 127.5, 127.0, 125.2, 98.9, 98.6, 86.3, 86.2, 74.7, 73.9, 73.0, 72.9, 72.8, 62.0, 61.9, 37.4, 37.3, 34.2, 33.8, 33.3, 30.6, 28.0, 25.4, 23.5, 23.4, 20.6, 19.4, 17.9, 17.1, 17.0, 16.9, 12.9; IR (neat) 3439, 2937, 2874, 1644, 1457, 1380, 1121, 1032, 742, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{40}O_4Na$ 427.2824, found 427.2817; $[\alpha]_D^{20}$ +6.1 (*c* 1.04, $CHCl_3$).

*4.1.5. Compound (S,R)-**27**.* Potassium hydride (30 wt % in mineral oil, 842 mg, 6.28 mmol) contained in a reaction tube for the microwave oven was washed with hexanes (2×2 mL) and dried with under a flow of dry nitrogen. 1,4-Dioxane (12 mL), **24** (277 mg, 0.68 mmol), and **25** (204 mg, 1.36 mmol) were added. The reaction mixture was heated to 110 °C in the microwave oven for 2 h, cooled in an ice-water bath, quenched with water (10 mL), and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:9; R_f 0.50) to give **27** (176 mg, 0.34 mmol, 50%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 5.66–5.40 (m, 2H), 5.19 (s, 1H), 5.12 (s, 1H), 4.66 (d, J=11.3 Hz, 1H), 4.60 (s, 2H), 4.55–4.51 (m, 1H), 4.47 (d, J=11.3 Hz, 1H), 4.05 (s, 1H), 4.00–3.90 (m, 1H), 3.90–3.77 (m, 2H), 3.56 (dd, J=9.3 Hz, 6.2 Hz, 0.5H), 3.52–3.39 (m, 2.5H), 3.34 (s, 3H), 3.19 (dd, J=9.3 Hz, 5.8 Hz, 0.5H), 3.11 (dd, J=9.4 Hz, 6.5 Hz, 0.5H), 2.55–2.38 (m, 1H), 2.38–2.07 (m, 1H), 1.89–1.61 (m, 7H), 1.60–1.43 (m, 5H), 1.43–1.21 (m, 3H), 1.15 (s, 3H), 1.12–1.01 (m, 1H), 0.91–0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 139.1, 129.6, 128.8, 128.2, 127.5, 127.4, 127.3, 126.5, 124.8, 113.0, 99.0, 98.8, 95.6, 83.0, 79.4, 73.7, 73.1, 73.0, 68.2, 62.2, 62.1, 55.2, 35.7, 34.2, 33.9, 33.4, 30.7, 28.1, 25.5, 20.4, 19.5, 18.8, 18.0, 17.1; IR (neat) 2941, 2874, 1723, 1453, 1380, 1271, 1115, 1002, 975, 711 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{31}H_{50}O_6Na$ 541.3505, found 541.3503. $[\alpha]_D^{20}$ +0.52 (*c* 1.2, $CHCl_3$).

*4.1.6. Compound (S,R)-**33**.* A solution of **27** (250 mg, 0.48 mmol), Grubbs catalyst, second generation (41 mg, 0.048 mmol), and dichloromethane (60 mL) was heated to 110 °C in the microwave oven for 20 min. The solvent was removed under vacuum and the crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:4; R_f 0.32) to give **33** (184 mg, 0.39 mmol, 80%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3–7.23 (m, 5H), 5.68–5.67 (m, 1H), 4.58–4.53 (m, 4H), 4.33 (d, J=11.6 Hz, 1H), 4.16 (d, J=16.7 Hz, 1H), 4.04 (d, J=16.7 Hz, 1H), 3.91–3.80 (m, 3H), 3.59–3.56 (m, 0.5H), 3.48–3.43 (m, 2.5H), 3.32 (s, 3H), 3.25–3.18 (m, 0.5H), 3.13–3.10 (m, 0.5H), 2.61–2.56 (m, 1H), 2.31 (dd, J=16.9 Hz, 7.1 Hz, 1H), 1.85–1.79 (m, 1H), 1.75–1.63 (m, 2H), 1.63–1.45 (m, 6H), 1.45–1.25 (m, 3H), 1.16 (s, 3H), 1.09–1.07 (m, 1H), 0.90 (2d, J=6.8 Hz, 2×1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.3, 128.1, 127.3, 127.2, 125.1, 98.9, 98.6, 95.0, 84.6, 79.5, 77.2, 76.9, 76.7, 71.7, 70.1, 62.6, 62.0, 55.1, 36.5, 34.1, 33.3, 30.6, 27.4, 25.4, 20.3, 19.5, 19.4, 18.1, 18.0, 17.1, 17.0, 16.9; IR (neat) 2937, 2869, 1629, 1457, 1375, 1147, 1100, 1092, 929, 737, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{28}H_{44}O_6Na$ 499.3036, found 499.3046. $[\alpha]_D^{20}$ +16.8 (*c* 0.72, $CHCl_3$).

*4.1.7. Compound (2S,3R)-**35**.* A solution of **33** (169 mg, 0.35 mmol), ethanol (17 mL), and hydrochloric acid (3 N, 2 mL, 6 mmol) was heated at reflux for 16 h and concentrated. The residue was redissolved in dichloromethane (5 mL), and triethylamine (336 μL, 2.4 mmol) and acetyl chloride (85 μL, 1.2 mmol) were added to the solution at 0 °C. The reaction mixture was stirred at rt for 14 h, diluted with dichloromethane (10 mL), washed with water (2×5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:4; R_f 0.39) to give **35** (96 mg, 0.22 mmol, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (5H, m), 5.74–5.78 (m, 1H), 4.54 (d, J=11.6 Hz, 1H), 4.40 (dd, J=12.5 Hz, 4.5 Hz, 2H), 4.34 (d, J=11.6 Hz, 1H), 4.08 (q, J=16.5 Hz, 2H), 3.94–3.90 (m, 1H), 3.84–3.80 (m, 1H),

3.43 (m, 1H), 2.64–2.57 (m, 1H), 2.36–2.30 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.81–1.69 (m, 1H), 1.60–1.52 (m, 2H), 1.47–1.40 (m, 1H), 1.40–1.21 (m, 2H), 1.17 (s, 3H), 1.14–1.07 (m, 1H), 0.90 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.8, 138.4, 136.9, 128.2, 127.4, 127.3, 126.6, 84.5, 84.4, 79.7, 71.8, 69.4, 66.9, 62.4, 36.6, 33.8, 32.5, 27.5, 20.9, 20.4, 18.0, 16.8, 16.7; IR (neat) 2937, 2879, 1738, 1644, 1557, 1453, 1375, 1235, 1089, 1027, 737, 695 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{36}O_6Na$ 455.2410, found 455.2415. $[\alpha]_D^{20}$ +18.1 (c 0.54, $CHCl_3$).

4.1.8. Compound ***37***. Triethylamine (158 μL, 0.69 mmol) and formic acid (21 μL, 0.69 mmol) were added to a solution of allylpalladium chloride dimer (3.5 mg, 0.009 mmol) and (2-biphenyl) di-*tert*-butylphosphine (11.3 mg, 0.047 mmol) in DMF (0.8 mL) under an atmosphere of nitrogen. The solution was stirred at rt for 5 min. Acetate **35** (80 mg, 0.18 mmol) in DMF (1.8 mL) was added to the solution of the palladium complex. After being stirred at 25 °C for 16 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL×2) and saturated $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:4) to give **37** (R_f 0.66, 14 mg, 0.037 mmol, 20%) and **42** (R_f 0.47, 37 mg, 0.1 mmol, 54%). Spectroscopic data of **37**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 4.76 (s, 1H), 4.71 (s, 1H), 4.60 (d, J=11.6 Hz, 1H), 4.38 (d, J=11.6 Hz, 1H), 4.14 (d, J=14.5 Hz, 1H), 4.05 (d, J=14.5, 1H), 3.93–3.90 (m, 1H), 3.83–3.80 (m, 1H), 3.24 (dd, J=9.9 Hz, 2.9 Hz, 1H), 2.45–2.37 (m, 1H), 2.17 (m, 1H), 2.02 (s, 3H), 1.99–1.90 (m, 1H), 1.79–1.64 (m, 2H), 1.62–1.50 (m, 1H), 1.50–1.40 (m, 1H), 1.37–1.26 (m, 3H), 1.16–1.10 (m, 4H), 0.89 (d, J=6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 150.0, 138.7, 128.2, 127.5, 127.4, 127.3, 109.2, 84.8, 80.1, 71.7, 69.4, 67.5, 39.7, 39.6, 33.9, 32.5, 30.6, 27.8, 20.9, 20.4, 17.3, 16.8, 16.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{34}O_4Na$ 397.2355, found 397.2361; $[\alpha]_D^{20}$ +1.3 (c 0.67, $CHCl_3$). Spectroscopic data of **42**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.72 (s, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.68 (s, 1H), 4.58 (d, J=11.2 Hz, 1H), 3.93–3.90 (m, 1H), 3.85–3.80 (m, 1H), 3.24 (dd, J=7.9 Hz, J=3.7 Hz, 1H), 2.30–2.19 (m, 1H), 2.12–2.07 (m, 1H), 2.03 (s, 3H), 1.79–1.73 (m, 1H), 1.71 (s, 3H), 1.71–1.65 (m, 2H), 1.59–1.43 (m, 2H), 1.41–1.32 (m, 3H), 1.16 (s, 3H), 1.15–1.07 (m, 1H), 0.90 (d, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 145.6, 138.5, 128.4, 128.2, 127.6, 127.5, 110.1, 86.6, 86.5, 75.0, 74.9, 69.4, 69.3, 37.1, 37.0, 34.9, 34.0, 33.9, 32.5, 28.9, 23.7, 23.6, 22.5, 20.9, 20.5, 16.8, 16.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{36}O_4Na$: 399.2511, found 399.2502.

4.1.9. Compound ***39***. A solution of **37** (14 mg, 0.037 mmol), potassium hydroxide (10 mg, 0.19 mmol), water (12 μL), and ethanol (0.5 mL) was stirred at rt for 16 h. The solvent was removed under vacuum, and the residue was diluted with dichloromethane (5 mL), washed with water (2×2 mL), dried (Na_2SO_4), and concentrated. The crude alcohol (12 mg) was redissolved in DMF (200 μL), and imidazole (10 mg, 0.14 mmol) and TBDPSCl (19 μL, 0.072 mmol) were added. The reaction mixture was heated in a 60 °C oil bath for 14 h, cooled to rt, diluted with ethyl acetate (5 mL), washed with water (2×1 mL) and saturated $NaCl_{(aq)}$ (1 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:20; R_f 0.40) to give **39** (11 mg, 0.019 mmol, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.63 (m, 4H), 7.39–7.23 (m, 11H), 4.76 (s, 1H), 4.70 (s, 1H), 4.59 (d, J=11.5 Hz, 1H), 4.37 (d, J=11.5 Hz, 1H), 4.12 (d, J=14.5 Hz, 1H), 4.03 (d, J=14.5 Hz, 1H), 3.50–3.46 (m, 1H), 3.44–3.37 (m, 1H), 3.29–3.26 (m, 1H), 2.46–2.40 (m, 1H), 2.19–2.14 (m, 1H), 1.97–1.90 (m, 1H), 1.77–1.68 (m, 1H), 1.65–1.60 (m, 2H), 1.59–1.21 (m, 4H), 1.13 (s, 3H), 1.05–1.0 (m, 1H), 1.03 (s, 9H), 0.89 (2d, J=6.7 Hz, 2×1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 138.7, 135.6, 134.1, 129.4, 128.2, 127.5, 127.4, 127.3, 109.2, 84.8, 84.7, 80.2, 71.7, 68.9, 67.5, 39.6, 35.7, 33.7, 30.6, 27.7, 26.8, 20.6, 20.5, 19.3, 17.6, 16.8; HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{50}O_3NaSi$: 593.3427, found 593.3424; $[\alpha]_D^{20}$ +7.4 (c 0.4, $CHCl_3$).

4.1.10. Compound ***41***. Ozone was bubbled into a solution of **39** (8 mg, 0.014 mmol) in dichloromethane (5 mL) at −78 °C until the solution became light blue. Dimethylsulfide (200 μL, 2.7 mmol) was added to the solution, and the reaction mixture was warmed to rt, stirred for 14 h, and concentrated. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexanes, 1:10; R_f 0.30) to give **41** (4 mg, 0.007 mmol, 50%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.39–7.23 (m, 11H), 4.60 (d, J=11.6 Hz, 1H), 4.36 (d, J=11.6 Hz, 1H), 4.11 (dd, J=18.6 Hz, 1.4 Hz, 1H), 3.92 (d, J=18.6 Hz, 1H), 3.49–3.40 (m, 2H), 3.39–3.34 (m, 1H), 2.69–2.63 (m, 1H), 2.54–2.49 (m, 1H), 2.13–2.06 (m, 1H), 1.86–1.77 (m, 1H), 1.69–1.42 (m, 3H), 1.41–1.17 (m, 4H), 1.13 (s, 3H), 1.03 (s, 3H), 0.90 (2d, J=6.5 Hz, 2×1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 137.9, 135.5, 134.0, 129.4, 128.2, 127.6, 127.5, 127.4, 83.0, 82.9, 80.6, 71.8, 70.5, 68.8, 39.5, 36.9, 35.6, 35.5, 33.6, 26.8, 22.3, 20.5, 20.4, 19.2, 16.9, 16.8; IR (neat) 2952, 2858, 1717, 1427, 1385, 1256, 1110, 742, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{36}H_{48}O_4NaSi$ 595.3220, found 595.3211. $[\alpha]_D^{20}$ −1.4 (c 0.14, $CHCl_3$); lit. +5.6 (enantiomer, c 1.0, $CHCl_3$).[4c]

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Supplementary data

Experimental procedures, and NMR spectra of the new compounds can be found in the online version, at doi:10.1016/j.tet.2011.10.023.

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