Studies on conformationally controlled reactions of α,β-unsaturated macrolides

Leena Kaisalo,* Jorma Koskimies and Tapio Hase

*University of Helsinki, Department of Chemistry, Laboratory of Organic Chemistry,
FIN-00014 University of Helsinki, Finland*

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Allylic oxidation of 13- to 15-membered simple α,β-unsaturated (ω − 1)-macrolides was observed to be highly diastereoselective. Also reduction and Grignard addition reactions of α,β-unsaturated γ-ketomacrolides proceeded with high diastereoselectivity. The selectivity is controlled by the preferred conformations of the macrocyclic rings. The Boltzmann distribution of the starting material conformations can be used to predict the diastereoselectivity of these reactions.

Introduction

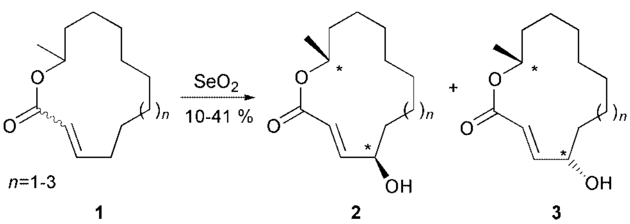
Conformational stereocontrol in macrocyclic compounds has been studied since 1981 when Still and Galynker published their investigations on the chemical consequences of conformation in macrocyclic compounds.[1] Conformationally controlled reduction and alkylation reactions have been used to generate chiral centers on the macrocyclic skeleton of some macrolide antibiotics and their analogs.[2] The high stereoselectivity of these reactions can be rationalized by molecular mechanics calculations. The conformational analysis of large ring compounds is difficult due to the large number of local energy minima. Vedejs and co-workers solved this problem by introducing the concept of local conformation effect according to which the analysis can be limited to the immediate vicinity of the functional group. They used this method to explain the selectivity of epoxidation and osmylation reactions in 10-membered rings.[3] Later Weiler and co-workers used the same method to rationalize the stereocontrol of alkylation and reduction reactions of 14-membered β-ketolactones.[4]

Functionalized macrocycles have three-dimensional structures which differ significantly from the normal rings in that sp^2 centers tend to lie perpendicular to the plane of the ring to minimize transannular non-bonded interactions. The reactions occur largely or perhaps exclusively from the peripheral face of the double bond.[1]

We have recently reported the synthesis and SeO_2 oxidation reactions of certain simple 13- to 15-membered α,β-unsaturated macrolides.[5] γ-Hydroxy and γ-oxo products were obtained from the latter reactions.

Reaction results

We now report that the SeO_2 oxidation of 13- to 15-membered simple α,β-unsaturated (ω − 1)-macrolides to the corresponding (2*E*)-γ-hydroxy macrolide compounds is highly stereoselective (Scheme 1). The major isomer **2** is obtained with 75–99% selectivity (d.e. ratios from 50 to over 98%). The diastereomeric ratios of the γ-hydroxy macrolide products **2**:**3** from the SeO_2 oxidation are collected in Table 1. The γ-hydroxy products **2** and **3** always have 2*E*-geometry even if the starting material was the 2*Z*-isomer.



1 **2** **3**

Scheme 1

Table 1 The diastereoselectivity of the macrolide γ-hydroxylation reactions

Ring size (**1**)	*n*	Diastereomeric ratio **2**:**3** by GLC
13*E*	1	89:11
13*Z*	1	81:19
14*E*	2	85:15
14*Z*	2	75:25
15*E*	3	>99:1
15*Z*	3	>99:1

The diastereomers **2** and **3** can be separated by GLC and they can be distinguished by ^1H NMR. The signals assigned to the H(3) of the diastereomers **2** have slightly (0.06–0.18 ppm) smaller chemical shifts compared to those of **3**. The vicinal coupling constants between H(3) and H(4) are larger for the diastereomers **2**, *e.g.* in the case of 13-membered macrolides **2**[6] and **3** ($n = 1$) the chemical shifts for H(3) are 6.89 and 7.05 ppm and the coupling constants are $J_{3,4}$ 7.0 and 4.4 Hz, respectively. The corresponding coupling constants, 9.0 and 5.5 Hz, calculated from the Karplus equation (Boltzmann average over the set of conformations within 20 kJ mol^{-1} of the minimum) are in reasonable agreement with the observed values. The conformations are obtained with MacroModel[7] using the Monte Carlo search and an MM2 force field (see below).

Along with the macrocyclic allylic alcohols we always isolated *E* and *Z* enones.[5] These enones were the main products if the reaction was performed in dry dioxane but the proportion of alcohol increased if some water was added to the reaction mixture.[8] In the case of 13- and 14-membered macrolides we also isolated the furanone derivative **4**, in 22% and 11% yield, respectively. The analogous furanone derivative was the only isolated oxidation product from the SeO_2 oxidation of the 12-membered homolog.[9]

We assume that the compound **4** is formed *via* an internal transesterification of the initially formed *Z* α,β-unsaturated alcohol **5** which was never isolated from the reaction mixture[5] (Scheme 2).

The reduction reactions of *E* α,β-unsaturated γ-oxo macrolides **6** were also highly diastereoselective (Scheme 3), the major

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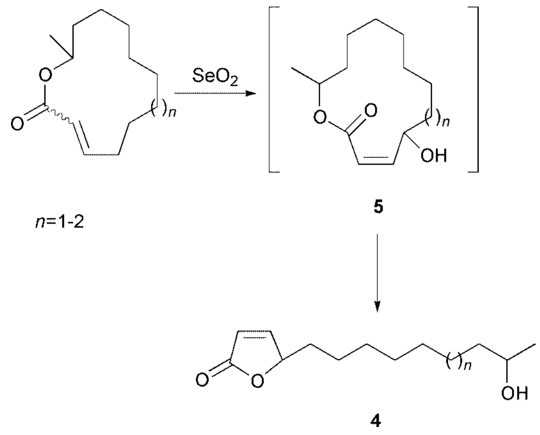
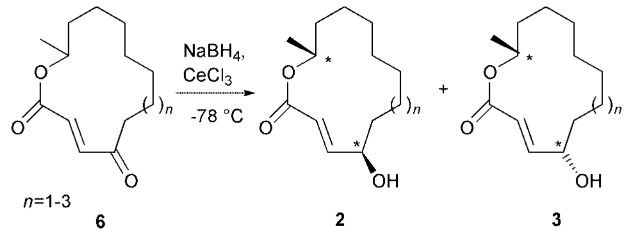
Table 2 $NaBH_4$–$CeCl_3$ reduction of the ketomacrolides **6**

Ring size (**6**)	*n*	Yield (%) (**2**) + (**3**)	Diastereomeric ratio **2**:**3** by GLC
13*E*	1	78	4:96
14*E*	2	91	18:82
15*E*	3	88	12:88



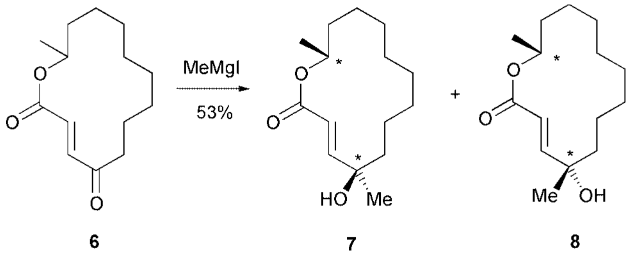
Scheme 2



Scheme 3

diastereomer from the $NaBH_4$–$CeCl_3$ reduction[10] being **3**. The results of the reduction reactions are shown in Table 2.

The stereoselectivity of the Grignard addition of MeMgI to the 14-membered ketolactone **6** ($n = 2$) was 14:86 (d.e. = 72%) (Scheme 4). We assume that the reaction on the carbonyl group occurs from the same side as the reduction, so the major product is tentatively assumed to be **8**.

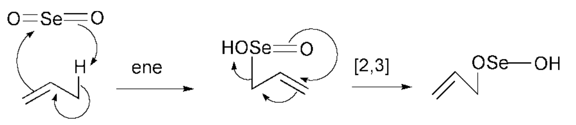


Scheme 4

Calculation results

Oxidation

The mechanism now generally accepted for SeO_2 allylic oxidation was proposed by Sharpless,[11] the pathway being an ene reaction followed by [2,3]-sigmatropic rearrangement (Scheme 5). Both steps consist of a six-electron pericyclic reaction. For the ene reaction to occur there must be in the transition state a parallel arrangement of the p-orbitals of the double bond carbons and the σ-orbital of the breaking C–H bond.[12]



Scheme 5

Table 3 The experimental and calculated ratios of oxidation products **2** and **3** from the *E* starting materials

Ring size (**1**)	*n*	Diastereomeric ratio **2**:**3** by GLC	Calculated ratio **2**:**3**
13*E*	1	89:11	84:16
14*E*	2	85:15	69:31
15*E*	3	>99:1	79:21

The diastereoselectivity of the oxidation depends on the selectivity of the ene reaction. In an attempt to rationalize the high selectivity the conformations of macrolides **1** were generated by MacroModel[7] using the Monte Carlo conformational search method and an MM2 force field. We did the conformational searches with 5000 Monte Carlo random steps (10 000 for 15-membered macrolides).[13] There are no reliable transition state parameters for SeO_2 oxidation in MacroModel so to approximate the transition state we decided to look at the low energy conformers of macrolides **1**, making the reasonable assumption that the transition state geometry is formed from the local minimum conformation by a relatively small change in geometry. The conformations of *E* unsaturated macrolides show clearly that the two faces of the olefinic π-system are different (Fig. 1). One face of the π-system is shielded by the CH_2-skeleton while the other is open.

When comparing the endocyclic torsional angles of the low energy conformations it was apparent that the reactive part of the molecule O–C(O)–C=C–C–C has only a few possible local conformations. The large number of local minima arise from the different orientations of the CH_2-chain. All the 13- to 15-membered *E* α,β-unsaturated macrolides **1** have the same lowest energy local conformation with respect to torsions O–C(O)–C=C–C–C.

In all the conformers, the allylic hydrogens as well as the methyl group are on the peripheral side of the ring. When SeO_2 approaches from this side it has two allylic hydrogens to choose from. The selectivity of the products depends on which of the two allylic hydrogens is able to produce the better overlap with the double bond π-orbitals. An approach from the opposite side will not lead to a reaction because there are no protons to abstract.

To predict the ratio of the two diastereomeric products we took a closer look at the structures from the conformational search which were within 10 kJ mol^{-1} of the minimum and in which the torsional angle between the double bond and either of the allylic hydrogens is $|90 \pm 40°|$. A larger deviation from the ideal (90°) would make the overlap between the orbitals in the transition state impossible. The relevant conformations[14] were divided into two groups according to their local conformation at the allylic position. Depending on which of the two allylic hydrogens is the leaving one, the product is either *R*S** or *S*S**. The diastereomeric ratio is derived simply by dividing the sum of concentrations of the structures leading to *R*S** by the total concentrations leading to *S*S**.

The concentrations were obtained from the Boltzmann factors calculated at 25 °C. Table 3 summarizes the results of the calculations of *E* α,β-unsaturated macrolides. The product ratios based on the ground state energies obtained from the molecular mechanics calculations give a reasonably good fit with experiment.

In predicting the product ratios of *Z* α,β-unsaturated macrolides a complication arises because the isomerization of the double bond has to take place. After the commencement of the ene-reaction step a 180° rotation about the α,β-bond enables the formation of an α,β-double bond of *E* geometry[15] and at the same time inverts the stereochemistry of the allylic carbon.

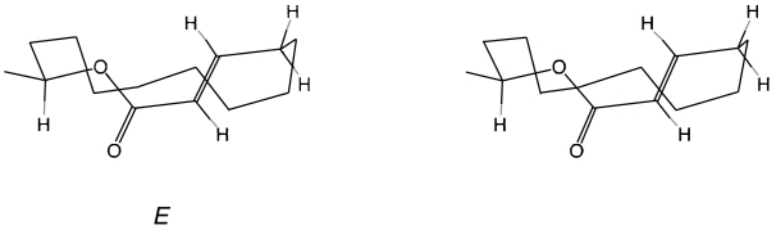


Fig. 1 Stereo view of the lowest energy conformer of *E* α,β-unsaturated 14-membered macrolide.

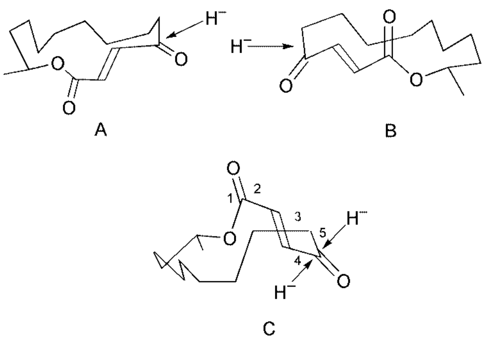


Fig. 2 The three local conformations of 14-membered ketolactone **6**.

The oxidation reaction is known to have a strong preference for *E*-allylic products[11,16] but in the case of *Z* **1** noticeable amounts of the furanone derivatives **4** or the *Z* ketones were isolated.[5] This indicates that the isomerization step is incomplete. Many of the low energy conformations of the 14*Z* and 15*Z* macrolides **1** have very close (*e.g.* 2.28 Å) contacts between the allylic hydrogen and the carbonyl oxygen whereas the 13*Z* **1** has only a few such conformations. These close contacts are associated with a strong downfield shift, 0.8 and 0.5 ppm, of one allylic hydrogen in the ^{1}H NMR spectra of 14*Z* and 15*Z* macrolides **1**, respectively. In the case of the 13*Z* **1** no such shift is observed.[5] The nature of the C–H · · · O interaction is known to be electrostatic and attractive[17] and so this interaction may hinder the rotation step. If we leave the conformations with close C–H · · · O contacts out of the calculations the results of 14*Z* and 15*Z* macrolides are in better accordance with the experimental values. The effect in the case of 13*Z* **1** is negligible. The calculated results are shown in Table 4.

Reduction

In order to explain the selectivity in the reduction reaction, as above for SeO_2 oxidation, a Monte Carlo conformational search was done for the γ-oxo macrolides **6** using an MM2 force field.[18] It has been suggested that an early transition state can account for the selectivities observed in the reduction of α,β-unsaturated ketones.[4b,19]

In the case of the 14-membered ketolactone **6** an inspection of the low energy conformations within 4.18 kJ mol^{-1} of the minimum shows that the conformations can be classified into three groups according to their local conformations about the carbonyl group (Fig. 2). The conformations in groups A and B have the carbonyl group perpendicular to the plane of the ring and the reaction has to occur from the exocyclic face as the other face is effectively blocked. The group A (12 conformations) will give the 4*S**13*S** alcohol **3** predominantly whereas the group B (four conformations) will give the diastereomeric product 4*R**13*S** **2**. The addition on the conformation C (one conformation) will furnish both diastereomeric products as the carbonyl is in a corner position and the steric environments of the two faces of the carbonyl are almost identical.

The predicted ratio of the diastereomeric products, calculated from the Boltzmann distribution of the conformations within 4.18 kJ mol^{-1} of the minimum gave the ratio 22 : 78 for the alcohols **2** : **3** which is in good agreement with the experimental ratio 18 : 82.

Table 4 The experimental and calculated ratios of oxidation products **2** and **3** from the *Z* starting materials

Ring size (**1**)	*n*	Diastereomeric ratio **2** : **3** by GLC	Calculated ratio[a] **2** : **3**	Calculated ratio[ab] **2** : **3**
13*Z*	1	81 : 19	81 : 19	86 : 14
14*Z*	2	75 : 25	23 : 77	74 : 26
15*Z*	3	>99 : 1	44 : 56	86 : 14

[a] The inversion of the stereocenter during isomerization has been taken into account. [b] Conformers with close allylic CH · · · O (<2.5 Å) contact omitted.

Table 5 The experimental and calculated ratios of reduction products **2** and **3**

Ring size (**6**)	*n*	Diastereomeric ratio **2** : **3** by GLC	Calculated ratio **2** : **3**
13*E*	1	4 : 96	26 : 74
14*E*	2	18 : 82	22 : 78
15*E*	3	12 : 88	23 : 77

The conformational analysis of 13- and 15-membered ketolactones was more straightforward as there were within 4.18 kJ mol^{-1} only six and five conformations, respectively, and none of them belonged to group C. The diastereomeric ratios were calculated as before and the results are summarized in Table 5.

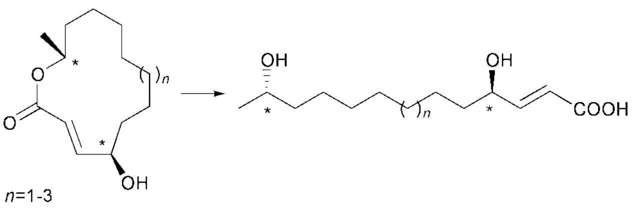
Conclusions

The macrolides have features which are not commonly shown by normal size rings. They have a large number of low energy conformations through which the reactions can occur. The sp^2 centers tend to stand perpendicular to the plane of the ring so that the other face of the sp^2 centers is effectively blocked by the CH_2-skeleton and the reactions occur from the peripheral side of the ring. Due to these features the reactions on macrolides are conformationally stereocontrolled.

Both diastereomers of *E* α,β-unsaturated γ-hydroxy macrolides **2** and **3** can be synthesized with high diastereoselectivity. The diastereoselectivity of the SeO_2 oxidation reaction is proportional to the number of low energy conformers which have an allylic hydrogen at a suitable angle with respect to the double bond. In the case of *E* α,β-unsaturated macrolides **1** the calculated ratios of the products **2** and **3** are in good agreement with the experimental values. The isomerization of the double bond after the ene reaction in the case of *Z* isomers **1** makes the situation more complex.

The selectivities of the reduction reactions of the ketomacrolides **6** are due to the attack of the anion at the carbonyl group from the more open exocyclic face of the macrocycles. This gives rise to product ratios that are closely related to the ground state conformational energies of the starting materials. The method of predicting the major product diastereomer simply by looking at the conformer distribution of the starting material conformations is very simple and neglects the Curtin–Hammett principle[20] yet still gives a reasonably good fit with the experimental results.

The macrolide oxidation, reduction and alkylation reactions described here will offer a way of effecting very remote asymmetric induction (1,9-, 1,10- or 1,11-) in the synthesis of long chain alkyl chain structures (Scheme 6).



Scheme 6

Experimental

The flash silica was Merck Kieselgel 60 (0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a Varian GEMINI-200 FT NMR spectrometer in $CDCl_3$. HRMS spectra were obtained with a JEOL JMS-SX102 mass spectrometer operating at 70 eV. GLC analyses were performed using an HP6890 gas chromatograph equipped with an HP-5 5% Phenyl Methyl Siloxane capillary column (15 m; 0.32 mm; 1.00 µm film thickness).

General procedure for SeO_2 oxidation

α,β-Unsaturated macrolide **1** was added to freshly sublimed SeO_2 (2 equiv.) in anhydrous dioxane. The mixture was refluxed and the reaction was followed by TLC. The cooled solution was filtered through a pad of Celite which was washed several times with Et_2O. The filtrate was evaporated and the crude product was flash chromatographed (silica, 1 : 9 EtOAc–CH_2Cl_2). The main product was **2**.

For the preparation and spectral data of products **2** (n = 1–3) and **6** (n = 2–3) see reference 5. To prepare the 13-membered homolog **6** (n = 1) we oxidized and protected the allylic position of the 2*E* double bond before the lactonization step.

(2*E*)-4-Oxotridec-2-en-12-olide 6 (*n* = 1). ^1H NMR (200 MHz, $CDCl_3$): δ 7.50 (1H, d, 15.8 Hz, CH=C–COO), 6.48 (1H, d, 15.8 Hz, C=CHCOO), 5.0–4.7 (1H, m, CH–O), 2.61 (1H, ddd, 17.3 Hz and 6.6 Hz and 3.8 Hz, CH_a–C=O), 2.38 (1H, ddd, 17.3 Hz and 9.8 Hz and 4.0 Hz, CH_b–C=O), 2.0–1.1 (12H, m), 1.34 (3H, d, 6.2 Hz, CH_3). ^{13}C NMR: 201.1 (C=O), 165.5 (C=O), 138.8 (C=C), 129.4 (C=C), 73.9 (C–O), 41.9, 35.2, 27.6, 26.6, 26.3, 23.3, 22.5, 20.6.

General procedure for $NaBH_4$ reduction

$CeCl_3 \cdot 7H_2O$ (1 equiv.) was added to α,β-unsaturated ketomacrolide **6** in EtOH. The mixture was cooled to −78 °C and 2 equiv. of $NaBH_4$ was added in small portions. After 0.5 h water was added to the cold reaction mixture followed by addition of 2 M HCl. The product was extracted with EtOAc, dried ($MgSO_4$) and evaporated. The main product was **3**.

(2*E*,4*S,12*S**)-4-Hydroxytridec-2-en-12-olide 3 (*n* = 1).** ^1H NMR (200 MHz, $CDCl_3$): δ 7.05 (1H, dd, 15.6 Hz and 4.4 Hz, $CH{=}CCO_2$), 6.02 (1H, d, 15.6 Hz, $C{=}CHCO_2$), 5.1–4.9 (1H, m, CH–O), 4.5–4.3 (1H, m, CH–O), 2.0–1.1 (18H, m, 7 × CH_2, OH, CH_3). ^{13}C NMR: 166.4 (C=O), 151.1 (C=C), 119.6 (C=C), 72.2 (C–O), 71.2 (C–O), 35.6, 34.2, 28.1, 28.1, 26.0, 22.9, 21.5 (7 × CH_2), 20.5 (CH_3). HRMS: 226.1559 found, 226.1569 required.

(2*E*,4*S,13*S**)-4-Hydroxytetradec-2-en-13-olide 3 (*n* = 2).** ^1H NMR (200 MHz, $CDCl_3$): δ 6.98 (1H, dd, 15.8 Hz and 5.0 Hz, $CH{=}CCO_2$), 6.04 (1H, d, 15.8 Hz, $C{=}CHCO_2$), 5.2–5.0 (1H, m, CH–O), 4.5–4.4 (1H, m, CH–O), 2.0–1.1 (20H, m, 8 × CH_2, OH, CH_3). ^{13}C NMR: 165.9 (C=O), 149.8 (C=C), 120.4 (C=C), 71.3 (C–O), 71.1 (C–O), 35.0, 34.4, 27.0, 26.8, 26.5, 26.0, 23.4, 22.4 (8 × CH_2), 20.4 (CH_3). HRMS: 240.1730 found, 240.1725 required.

(2*E*,4*S,14*S**)-4-Hydroxypentadec-2-en-14-olide 3 (*n* = 3).** ^1H NMR (200 MHz, $CDCl_3$): δ 6.93 (1H, dd, 15.8 Hz and 4.4 Hz, $CH{=}CCO_2$), 6.03 (1H, d, 15.8 Hz, $C{=}CHCO_2$), 5.2–5.0 (1H, m, CH–O), 4.6–4.4 (1H, m, CH–O), 2.0–1.1 (22H, m, 9 × CH_2, OH, CH_3). ^{13}C NMR: 165.5 (C=O), 149.6 (C=C), 120.6 (C=C), 71.4 (C–O), 70.9 (C–O), 34.4, 29.5, 27.6, 27.3, 26.9, 26.7, 26.2, 23.9, 20.9 (9 × CH_2), 20.2 (CH_3).

(2*E*)-4-Hydroxy-4-methyltetradec-2-en-13-olide 7 and 8

0.2 mmol of 1 M MeMgI in anhydrous Et_2O was added to 0.04 g (0.17 mmol) of (2*E*)-4-oxotetradec-2-en-13-olide in 1 mL of anhydrous Et_2O under Ar at r.t. After 1 h at r.t. the reaction mixture was cooled to 0 °C and sufficient saturated NH_4Cl solution was added to dissolve the precipitate. After extraction with Et_2O the organic layer was washed with brine and dried ($MgSO_4$). Evaporation and flash chromatography (silica, 1 : 9 EtOAc–CH_2Cl_2) afforded 19 mg (44%) of the major diastereomer and 3.8 mg (9%) of the minor diastereomer.

Major product: ^1H NMR (200 MHz, $CDCl_3$): δ 6.98 (1H, d, 15.8 Hz, CH=C–COO), 6.00 (1H, d, 15.8 Hz, C=CH–COO), 5.1–4.9 (1H, m, CH–O–C=O), 1.9–1.0 (23H, m). ^{13}C NMR: 166.5 (C=O), 154.1 (C=C), 119.3 (C=C), 73.7 (C–O), 71.3 (C–O), 41.1, 34.5, 28.2, 27.7, 27.3, 26.6, 25.8, 23.3, 22.4, 20.3 (2 × CH_3, 8 × CH_2). HRMS: 254.1878 found, 254.1882 required.

Minor product: ^1H NMR (200 MHz, $CDCl_3$): δ 6.92 (1H, d, 16.0 Hz, CH=C–COO), 6.03 (1H, d, 16.0 Hz, C=CH–COO), 5.1–5.0 (1H, m, CH–O–C=O), 1.9–1.0 (23H, m). ^{13}C NMR: 165.6 (C=O), 153.3 (C=C), 119.9 (C=C), 73.6 (C–O), 71.2 (C–O), 41.7, 34.5, 28.4, 28.1, 27.2, 27.0, 26.8, 23.9, 23.3, 20.8 (2 × CH_3, 8 × CH_2). HRMS: 254.1867 found, 254.1882 required.

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produce a lower minimum than already found by stochastic searches.

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