Intramolecular [4 + 3] cycloadditions — Stereochemical issues in the cycloaddition reactions of cyclopentenyl cations — A synthesis of (+)-dactylol[1]

Michael Harmata, Paitoon Rashatasakhon, and Charles L. Barnes

Abstract: Five cyclopentanones were prepared for the purpose of examining the effects of stereogenic centers on the course of the intramolecular [4 + 3] cycloaddition reactions of cyclopentenyl cations. One substrate reacted with very high levels of diastereoselectivity and was converted to (+)-dactylol. The cyclopentenone without stereogenic centers on the tether or the five-membered ring gave two cycloadducts, the endo isomer being only slightly favored over the exo. Other substrates reacted with generally good to poor stereoselectivity. An epimer of the substrate leading to (+)-dactylol afforded all possible isomers of the cycloadduct with relatively poor stereoselectivity.

Key words: cycloaddition, total synthesis, dactylol.

Résumé : On a préparé cinq cyclopentanones dans le but d'examiner les effets des centres stéréogènes sur le cours des réactions de cycloaddition [4 + 3] intramoléculaires des cations cyclopentényles. Un substrat réagit avec des degrés élevés de diastéréosélectivité et conduit à la formation du (+)-dactylol. La cyclopenténone sans centres stéréogènes sur la chaîne latérale ou sur le cycle à cinq chaînons conduit à la formation de deux cycloadduits dans lesquels l'isomère endo est légèrement favorisé par rapport à l'isomère exo. D'autres substrats réagissent avec des stéréosélectivités qui vont généralement de bonnes à mauvaises. Un épimère du substrat qui conduit au (+)-dactylol a permis d'isoler tous les isomères possibles du cycloadduit avec une stéréosélectivité relativement faible.

Mots clés : cycloaddition, synthèse totale, dactylol.

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Introduction

The intramolecular [4 + 3] cycloaddition reaction of allylic cations and dienes has been shown to be a powerful route to polycyclic compounds (1). One variation on this theme involves the use of cyclic cations in the cycloaddition reaction. Appropriate modifications of the cycloadducts from such reactions can then provide useful routes to natural products (2). We and others realized the potential for this process in the context of the synthesis of cyclooctanoids (3). We recently reported a total synthesis of (+)-dactylol based on this chemistry (2*c*). This report is a more detailed description of that work, including studies to evaluate the effects of various stereocenters on the course of the cycloaddition reaction.

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M. Harmata,[2] P. Rashatasakhon, and C.L. Barnes. Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA.

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[2]Corresponding author (e-mail: harmatam@missouri.edu).

Results and discussion

Diene synthesis

The basic approach for the preparation of substrates for this study consisted of the alkylation of cyclopentanone enolates with diene-containing electrophiles. The synthesis of the dienes used is shown in Scheme 1. Treatment of **1a**–**1c** with $TMSCH_2MgCl$–$CeCl_3$ followed by iodide formation afforded **3a**–**3c** in excellent yields (4, 5).

Ester **1a** was prepared by a literature procedure (6). Esters **1b** and **1c** were prepared as shown in Scheme 2. Protection of 1,4-butanediol with allyl bromide followed by oxidation gave the acid **5** in 69% yield from **4**. Oxazolidinones were formed from **5** in standard fashion and alkylated with high stereoselectivity and in good yields to afford **6b** and **6c**. Reduction with LAH gave the alcohols **7b** and **7c** in excellent yields. Swern oxidation, Wittig homologation, and deprotection (7) afforded esters **1b** and **1c** in 81% and 77% yields, respectively.

Preparation of cycloaddition substrates

Cycloaddition substrates were easily prepared by alkylation. For example, the reaction of **8** with potassium carbonate in the presence of **3a** afforded the alkylation product **9** in good yield. This was converted to the ketone **11** in 66% yield via reaction with potassium cyanide in hot DMSO

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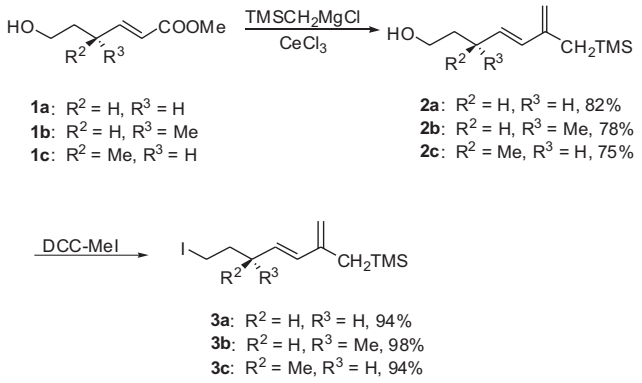
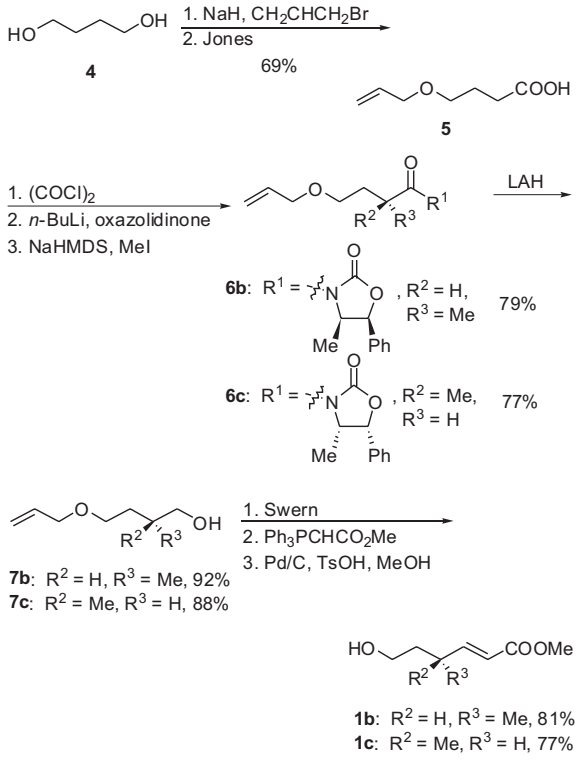
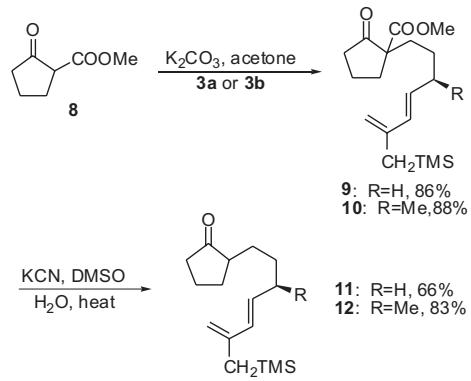
Scheme 1.



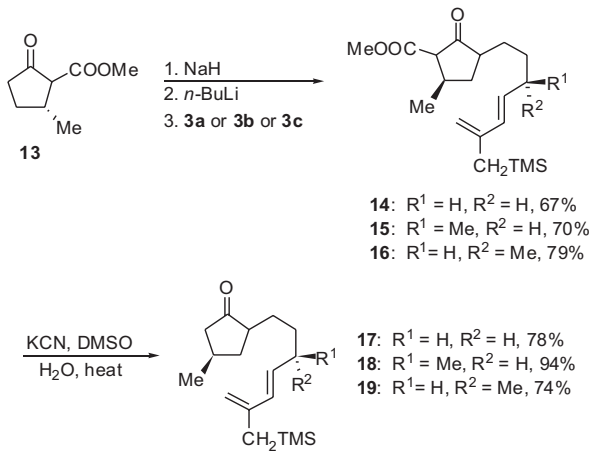
Scheme 2.



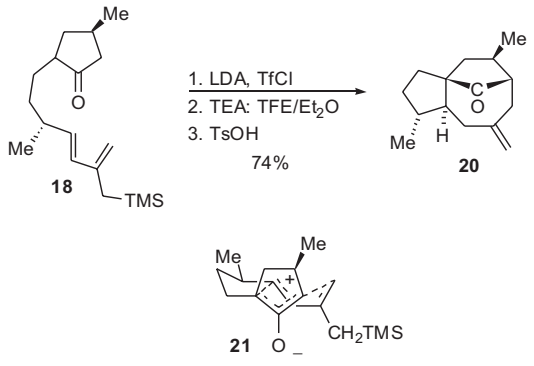
Scheme 3.



Scheme 4.



Scheme 5.



(8). Ketone **12** was prepared in a similar fashion in 73% overall yield (Scheme 3).

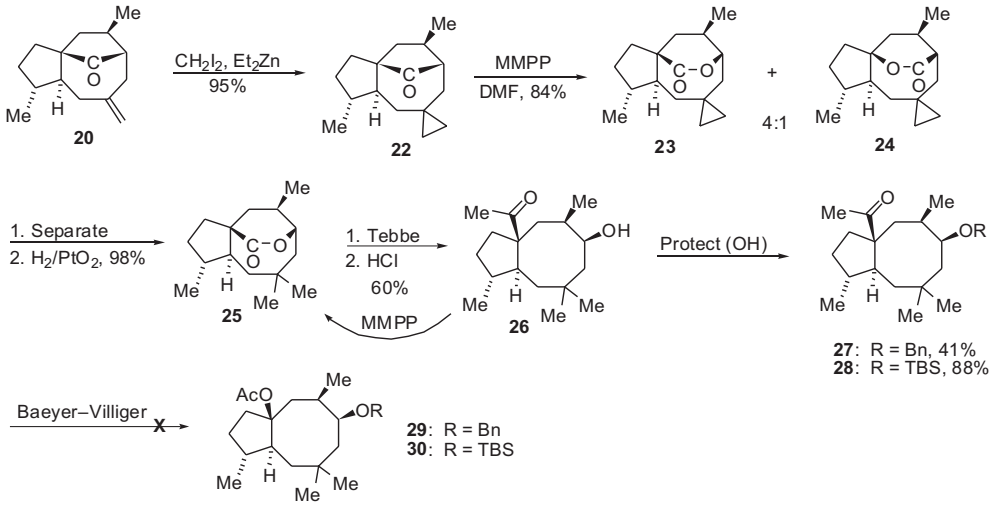
The ketoester **13** was readily prepared from (*R*)-pulegone by a known procedure (9). Dianion formation followed by alkylation and decarboalkoxylation afforded cycloaddition substrates **17**–**19**, as shown in Scheme 4.

The synthesis of (+)-dactylol

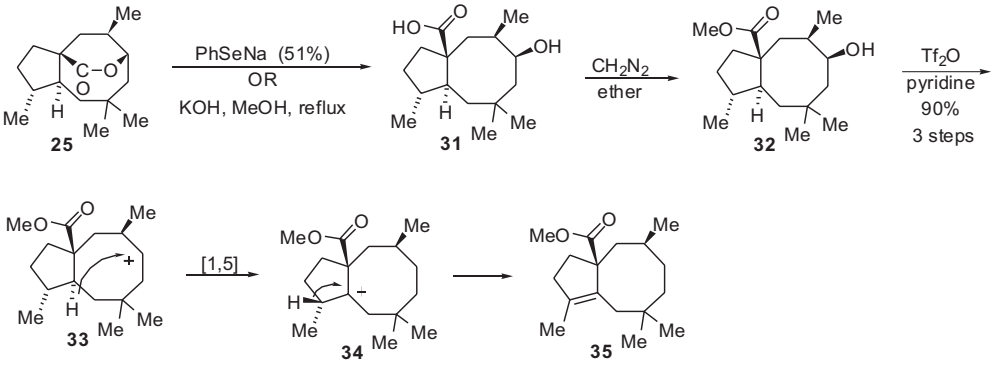
We begin with the synthesis of dactylol, since that was indeed the first cycloaddition in this series that we examined. Treatment of **18** with Lithium diisopropylamide (LDA) and reacting the resultant enolate with triflyl chloride gave an α-chloroketone. This was not characterized but immediately subjected to typical cycloaddition conditions: stirring at –78 °C to room temperature in a 1:1 mixture of ether and trifluoroethanol in the presence of 3 equiv. of triethylamine (Scheme 5). Even though the purification of the cycloadduct could be carried out at this stage, we found that some desilylation and double bond migration occurred during the chromatography on silica gel.

Therefore, the crude product was subsequently treated with tosic acid to give rise to alkene **20** as a 25:1 mixture of isomers in 74% yield for the three steps. The diastereomeric ratio was determined by GC and integration of the olefinic region of the ^{1}H NMR of a crude product mixture. The minor isomer has not been characterized. The rationalization for the favorable stereochemical outcome is depicted in structure **21**. We anticipated that the diene would approach the dienophile in an endo fashion on the less-hindered face of the dienophile. In addition, the methyl group on the tether

Scheme 6.



Scheme 7.



would occupy a pseudoequatorial orientation on the puckered, incipient five-membered ring with the diene oriented so as to minimize gauche interactions.

The next stage of the synthesis is shown in Scheme 6. Simmons–Smith cyclopropanation of **20** produced **22** in 95% yield. The Baeyer–Villiger reaction of **22** with MMPP in DMF afforded a 4:1 mixture of two regioisomers after purification. Surprisingly, the major product was that resulting from the migration of the less substituted carbon atom. Attempts to alter the regioselectivity using a variety of reaction conditions were unsuccessful, as some reagents gave higher regioselectivity but lower yields of the products.[3] Studies we have conducted suggest that the methyl substituent on the five-membered ring has a major, but not exclusive, influence on the regiochemistry of the reaction (10). The major isomer **23** was separated, and the cyclopropane ring was cleaved by hydrogenolysis to afford **25** in 98% yield. The structure and relative stereochemistry were established by X-ray crystallography.

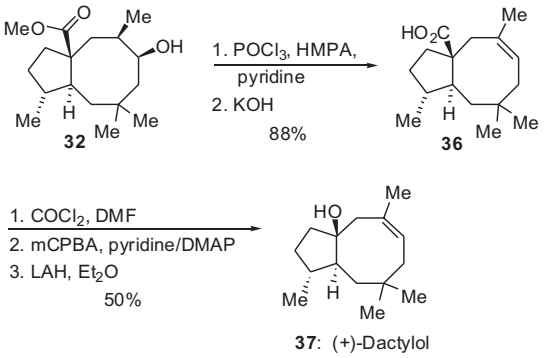
Our first attempt to convert **25** into dactylol began with a methylenation reaction using Tebbe's reagent (11). Hydrolysis of the resultant enol ether afforded the ketone **26**, whose hydroxy group could be protected with either a benzyl or TBS group. We anticipated that a Baeyer–Villiger oxidation of either of these species would afford the corresponding acetate **29** or **30**.[4] Unfortunately, no reaction occurred between either **27** or **28** and MMPP, *m*-CPBA, or TFAA-H_2O_2 after a 24 h period at room temperature. Treatment of **26** with MMPP afforded lactone **25** (10). We also attempted a reaction between lactone **25** and sodium phenylselenide and expected to obtain a system suitable for further elaboration to (+)-dactylol. However, the hydroxy acid **31** was obtained as the sole product in 51% yield, via an apparent hydrolysis reaction. Even though this result was not satisfactory, it proved the existence and stability of the hydroxycarboxylic acid **31**, which became significant.

Thus, the next sequence to (+)-dactylol began with a hydrolysis of lactone **25** using KOH in refluxing aqueous methanol and esterification of the corresponding hydroxy acid with diazomethane (Scheme 7). The next challenging step was the introduction of the double bond in dactylol by dehydration of **32**. Regioselectivity was a problem, as were side reactions. For example, treatment of **32** with $POCl_3$ in pyridine, Tf_2O in pyridine, or Martin's sulfurane resulted in

[3] Reagent, ratio **23**:**24**, solvent, temperature, time, yield: (*a*) *m*-CPBA–$NaHCO_3$, 6:1, CH_2Cl_2, RT, 5 d, 67%; (*b*) TFAA–H_2O_2, 5:1, CH_2Cl_2, 0 °C – RT, 3 d, 36%; (*c*) *m*-CPBA–TFA, 4:1, CH_2Cl_2, 0 °C–rt, 48 h, 53%; (*d*) peracetic acid – NaOAc, 9:1, AcOH, RT, 48 h, 31%; (*e*) MMPP, 4:1, DMF, RT, 48 h, 84%.

[4] Without protection of the alcohol group, the Baeyer–Villiger reaction proceeded by an unexpected course. See ref. 10.

Scheme 8.



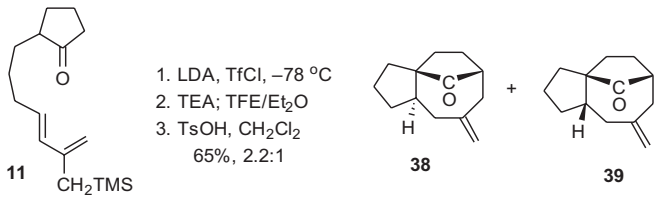
the formation of a compound identified as **35**. Presumably, these reagents induced cation formation, which was followed by a 1,5-transannular hydride shift to form **34**, and subsequent elimination to give tetra-substituted alkene **35**, whose structure was determined based on spectroscopic and analytical data. The ^{1}H NMR spectrum showed no signal for olefinic protons. The most downfield peak appeared at 3.59 ppm as a singlet, which corresponded to the methyl ester. There was also a singlet peak that integrated for three protons at 1.65 ppm, suggesting the presence of a methyl substituent on an olefin. The ^{13}C NMR spectrum confirmed the existence of ester and alkene (δ: 177.3, 136.9, 134.7).

By taking advantage of the dehydration procedure developed by Trost and Jungheim (12), we were able to overcome this problem (Scheme 8). Phosphorus oxychloride ($POCl_3$) was added to a solution of **32** in HMPA with slow heating from room temperature to 50 °C. After the white precipitate that formed dissolved, pyridine was added and heating was continued to 100 °C at which point the dehydration was complete. Subsequent hydrolysis of the sterically hindered methyl ester group using KOH in DMSO provided **36** as a single product (based on crude ^{1}H NMR) in 84% yield. At this point, we found that typical acid chloride formation procedures failed to give the acid chloride of the hindered acid **36**.[5] However, upon treatment with DMF and phosgene in refluxing toluene, **36** was cleanly converted to the corresponding acid chloride (13). In a benzene solution containing pyridine and DMAP, this acid chloride reacted with mCPBA to form a mixed anhydride, which rearranged upon stirring for 24 h at room temperature to a mixed carbonate with retention of configuration (14). Reduction of the mixed carbonate with LAH then afforded (+)-dactylol in 50% overall yield from **36**. The spectral, analytical, and optical rotation data were consistent with those reported in the literature (15).

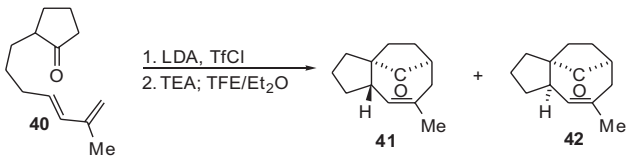
Simple diastereoselectivity

After the successful synthesis of (+)-dactylol, we decided to examine the influence of all stereocenters on the course of the reaction. First, however, we looked at simple diastereoselectivity. Past experience suggested that the intramolecular [4 + 3] cycloaddition reaction of cyclopentenyl cations with tethered butadienes would proceed with only a slight simple diastereoselectivity in favor of the endo product (3*b*). This was indeed the case.

Scheme 9.



Scheme 10.



The ketone **11** was treated with LDA and TfCl to furnish the corresponding α-chloroketone, which was subjected to the [4 + 3] cycloaddition and desilylation reactions (Scheme 9). Two diastereomeric cycloadducts (**38** and **39**) were obtained in 65% yield in a ratio of 2.2:1. The product ratio was determined by gas chromatographic analysis and integration of the crude product ^{1}H NMR spectrum. After purification by flash chromatography on silica gel, the major product was treated with excess $NH_2OH{\cdot}HCl$ and KOH in refluxing ethanol to form an oxime derivative. Recrystallization of this oxime from hexane and EtOAc afforded crystals of suitable quality for single crystal X-ray crystallographic analysis. Thus, the major product was assigned as the endo isomer **38**. It should be noted that cycloadditions of this type appear to take place under kinetic control.

We have examined simple diastereoselectivity computationally for the conversion of **40** to **41** and **42**. We found that while the lowest energy transition state corresponds to the endo product **41**, other transition state structures that lead to the exo product are close in energy, and thus, for unsubstituted systems at least, simple diastereoselectivity should not ever be expected to be substantial (Scheme 10) (16).

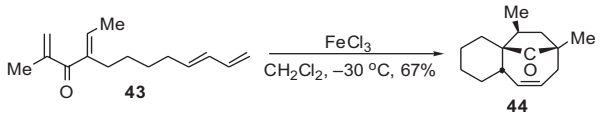
It is interesting to note that West and co-workers (3*a*) have reported very high simple diastereoselectivity in the formation of **44** via a domino Nazarov – [4 + 3] cycloaddition process as shown in Scheme 11. It is clear that many new features of this aspect of the intramolecular [4 + 3] cycloaddition reaction of cyclopentenyl cations remain to be uncovered.

Relative stereoselection I — Cycloaddition of 12

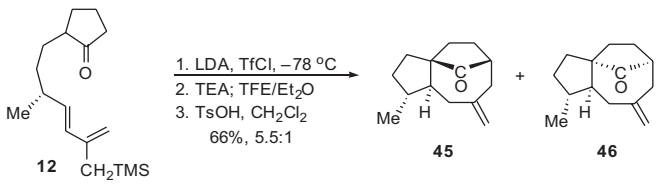
The introduction of a stereogenic center in the tether joining the diene and dienophile in these reactions introduces a new complication. Our goal in pursuing the cycloaddition of **12** was essentially to discover the impact of the stereocenter on the course of the reaction in an effort to elucidate which of the stereocenters in **18** had a more profound impact on the stereochemical outcome on that compound's cycloaddition.

[5] For example, stirring the solution of **36** in hexane with 3 equiv. of oxalyl chloride or heating a hexane solution of **36** with excess thionyl chloride resulted in no change.

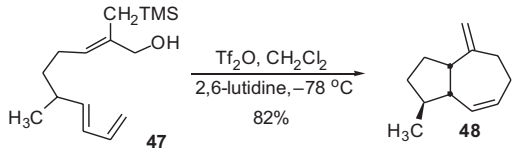
Scheme 11.



Scheme 12.



Scheme 13.



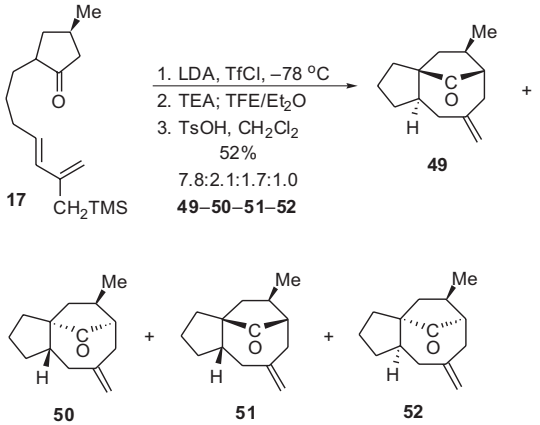
Cycloaddition of **12** afforded four products, only two of which, **45** and **46**, could be cleanly isolated (Scheme 12). Gas chromatographic analysis of the crude reaction mixture indicated a product ratio of 47.2(**45**):8.1(**46**):1:2.3. The major product of the reaction was **45**, as expected on the basis of the small but real endo preference observed in these systems and a report by Giguere and co-workers (17) on relative diastereoselection in intramolecular [4 + 3] cycloadditions. In that paper, Giguere and co-workers (17) reported that treatment of **47** with triflic anhydride afforded cycloadduct **48** as the major product of the reaction (Scheme 13). Regardless of the mechanistic basis for the outcome, one could assume that stereogenic centers adjacent to dienes would produce similar stereochemical outcomes in other intramolecular [4 + 3] cycloaddition reactions. This is what is observed in the formation of **45** and **46**. The structure of both compounds was established by X-ray analysis of the corresponding oximes.[6]

Relative stereoselection II — Cycloaddition of 17

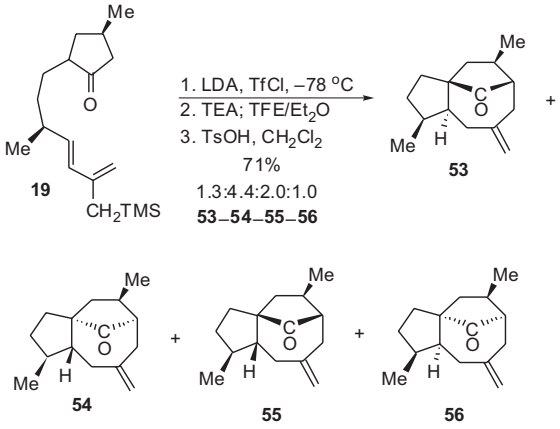
The cycloaddition reaction of **17** was anticipated to be reasonably selective. Endo–exo selectivity was not expected to be high but facial selectivity was expected to be reasonable, the diene approaching the less hindered face of the dienophile (i.e., on the face opposite the methyl substituent). There is a reasonable amount of precedent for this in the literature (18).

Surprisingly, the reaction produced all four possible isomeric products (**49**–**52**) in 52% yield overall from ketone **17** (Scheme 14). Gas chromatographic analysis of the crude product mixture suggested that the products were formed in a ratio of 7.8:2.1:1.7:1.0. They were separated by flash chromatography on silica gel and individually transformed into their oxime derivatives. Consistent with other data, the major

Scheme 14.



Scheme 15.



products were those derived from the transition states having the diene approaching from the opposite side of the methyl group on the stereogenic center. However, the level of facial selectivity in this reaction was approximately 3:1, while the endo–exo ratio was 3.4:1. The low level of facial selectivity is surprising, but larger substituents at the stereogenic centers should produce a better result.

Cycloaddition of 19 — The mismatched case

The last [4 + 3] cycloaddition in this study was the reaction of ketone **19**. Since the stereogenic center on the cyclopentanone remained the same (*R*) while the one on diene was switched from (*R*) to (*S*) compared with ketone **18**, we expected to see the diastereomer of **20** formed as the major isomer. In fact, the reaction produced all four isomers of cycloadduct (**53**–**56**) in 71% yield in a ratio of 1.3:4.4:2.0:1.0 (Scheme 15). Each product was purified, characterized, and converted into an oxime derivative, and the stereochemical assignment was made using X-ray crystallography. The major isomer (**54**) derived from a transition state having an endo approach of the diene with a tether conformation that minimized gauche interactions. However, at-

[6] The oxime derived from **46** gave poor quality X-ray data. Finding a suitable crystal was problematic and the one found turned out to be racemic, in spite of the fact that the bulk sample was clearly enantiomerically enriched based on optical rotation data. However, the data were sufficient to establish the relative stereochemistry.

tack occurred on what appears to be the more sterically hindered face of the oxyallylic cation intermediate.

Surprisingly, the overall facial selectivity in this case, (**53** + **55**):(**54** + **56**), was 1:1.6 in favor of the products derived from the approach of the diene to the more hindered face of the cyclopentanone. The endo–exo ratio, (**53** + **54**):(**55** + **56**) was 1.9:1 in favor of endo products. The relative stereoselectivity (**53** + **56**):(**54** + **55**) was 1:2.8 in favor of the products having a cis relationship between the angular hydrogen and the methyl group on the newly formed five-membered ring.

Conclusion

The intramolecular [4 + 3] cycloaddition of cyclopentenyl cations to dienes is a useful route to cyclooctanoids. High levels of stereocontrol in this reaction are possible, but it is clear that effects that might appear to be cooperative need not be and that further studies of these cycloadditions will be necessary to achieve results that are more generally suitable for applications in synthesis. This conclusion is true for acyclic dienes tethered to cyclopentenyl cations. High levels of simple diastereoselection are possible with tethered furans (3). Whether this inherent selectivity can be used to produce high levels of relative stereocontrol remains to be seen. We plan to perform further work to solve the problems that exist and continue to apply the methodology to the synthesis of cyclooctanoids. Further results will be reported in due course.[7]

Experimental

General procedure for Peterson olefination: synthesis of 2a–2c

A 500 mL round-bottomed flask was charged with powdered cerium(III) chloride heptahydrate ($CeCl_3$-$7H_2O$, 13.02 g, 34.96 mmol). The flask was immersed in an oil bath and evacuated to a full vacuum (about 0.1 mmHg (1 mmHg = 133.322 4)). The solid was magnetically stirred as the flask was heated at 150 °C for 2 h. After the flask was cooled to room temperature, it was vented to the atmosphere and quickly purged with a steam of argon for 30 s. The flask was capped with a rubber septum and 60 mL of THF was added. The white suspension was stirred at room temperature for 1 h, cooled to –78 °C in a dry ice – 2-propanol bath, and a 1 mol/L solution of trimethylsilylmethylmagnesium chloride (35 mL, 35 mmol) was added over a period of 15 min. After the cold mixture was stirred for an additional 15 min, 9.99 mmol of **1a**, **1b**, or **1c** was added dropwise and the mixture was allowed to warm slowly to room temperature over a period of 3 h. The reaction was quenched with ice-cold 1 mol/L HCl (60 mL) and stirred for 5 min. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution (100 mL), dried over magnesium sulfate, filtered, and the solvents were removed by rotavap. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1).

6-Trimethylsilylmethyl-hepta-4,6-dien-1-ol (2a)

Yield: 82%, colorless oil. IR (neat, cm^{-1}): 3353 (ms), 2947 (s), 1252 (s), 859 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.09 (d, *J* = 15.6 Hz, 1H), 5.58 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.78 (d, *J* = 1.5 Hz, 1H), 4.66 (s, 1H), 3.68–3.61 (m, 2H), 2.18 (q, *J* = 7.3 Hz, 1H), 1.77 (br t, *J* = 4.5 Hz, 1H), 1.72–1.61 (m, 2H), 1.69 (s, 2H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 143.7, 133.6, 129.7, 112.0, 62.3, 32.3, 29.0, 22.1, –1.2. HR-MS (EI) calcd. for $C_{11}H_{20}OSi$ (M^+): 198.1440; found: 198.1438.

(3R)-Methyl-6-trimethylsilylmethyl-hepta-4,6-dien-1-ol (2b)

Yield: 78%, colorless oil. $[\alpha]^{20}_D$ –24.42 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3334 (m), 2957 (s), 2929 (m), 2898 (m), 1596 (w), 1422 (w), 1250 (m), 1157 (m), 1054 (m), 967 (m), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.07 (d, *J* = 15.7 Hz, 1H), 5.45 (dd, *J* = 8.3, 11.3 Hz, 1H), 4.80 (d, *J* = 1.9, 1H), 4.68 (s, 1H), 3.66 (br s, 1H), 2.37 (sept, *J* = 7.1 Hz, 1H), 1.70 (s, 2H), 1.66–1.35 (m, 2H), 1.35 (br s, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7, 135.7, 132.0, 112.3, 61.2, 39.8, 34.0, 22.1, 21.0, –1.2. Anal. calcd. for $C_{12}H_{24}O_3Si$: C 67.86, H 11.39; found: C 67.92, H 11.47.

(3S)-Methyl-6-trimethylsilylmethyl-hepta-4,6-dien-1-ol (2c)

Yield: 75%, colorless oil. $[\alpha]^{20}_D$ +26.67 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3378 (s), 2957 (s), 2877 (s), 1459 (m), 1420 (m), 1380 (m), 1254 (s), 1055 (s), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.07 (d, *J* = 15.7 Hz, 1H), 5.45 (dd, *J* = 8.3, 11.3 Hz, 1H), 4.80 (d, *J* = 1.9, 1H), 4.68 (s, 1H), 3.66 (br s, 1H), 2.37 (sept, *J* = 7.1 Hz, 1H), 1.70 (s, 2H), 1.66–1.35 (m, 2H), 1.35 (br s, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7, 135.7, 132.0, 112.3, 61.2, 39.8, 34.0, 22.1, 21.0, –1.2. HR-MS (EI) calcd. for $C_{12}H_{24}OSi$ (M^+): 212.1596; found: 212.1610.

General procedure for conversion of alcohols to iodides: synthesis of 3a–3c

To a solution of **2a**, **2b**, or **2c** (4.70 mmol) in THF (47 mL) was added 9.42 mmol of DCC-MeI salt. The mixture was stirred in an oil bath at 35 °C for 6 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (100% hexane). Due to the instability of the products, the characterizations were performed by NMR and IR only.

(7-Iodo-2-methylene-hept-3-enyl)-trimethylsilane (3a)

Yield: 94%, colorless oil. IR (neat, cm^{-1}): 3078 (w), 2945 (s), 2896 (s), 1597 (m), 1423 (m), 1241 (m), 1155 (s), 967 (m), 846 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.12 (d, *J* = 15.7 Hz, 1H), 5.51 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.81 (d, *J* =

[7] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5104. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 282839–282845 and 282856 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

2.0 Hz, 1H), 4.69 (s, 1H), 3.19 (t, J = 6.9 Hz, 2H), 2.21 (q, J = 7.0 Hz, 2H), 1.92 (quint, J = 7.0 Hz, 2H), 1.69 (d, J = 0.7 Hz, 2H), –0.48 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 143.6, 134.6, 128.0, 112.5, 33.3, 33.1, 22.1, 6.3, –1.2.

(7-Iodo-(5R)-methyl-2-methylene-hept-3-enyl)-trimethylsilane (3b)

Yield: 98%, colorless oil. $[\alpha]^{20}_D$ –43.94 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3078 (w), 2955 (s), 2927 (m), 2897 (m), 1597 (m), 1422 (m), 1249 (s), 1158 (m), 969 (m), 851 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.12 (d, J = 15.7 Hz, 1H), 5.35 (dd, J = 8.4, 15.6 Hz, 1H), 4.84 (d, J = 1.9 Hz, 1H), 4.71 (s, 1H), 3.23–3.09 (m, 2H), 2.35 (sept, J = 6.8 Hz, 1H), 1.90–1.80 (m, 2H), 1.70 (s, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.5, 134.0, 132.9, 112.7, 40.6, 38.0, 22.1, 20.3, 4.9, –1.2.

(7-Iodo-(5R)-methyl-2-methylene-hept-3-enyl)-trimethyl silane (3c)

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +39.71 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3079 (w), 2952 (s), 2927 (m), 2887 (m), 1594 (m), 1421 (m), 1252 (s), 1160 (m), 970 (m), 853 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.12 (d, J = 15.7 Hz, 1H), 5.35 (dd, J = 8.4, 15.6 Hz, 1H), 4.84 (d, J = 1.9 Hz, 1H), 4.71 (s, 1H), 3.23–3.09 (m, 2H), 2.35 (sept, J = 6.8 Hz, 1H), 1.90–1.80 (m, 2H), 1.70 (s, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.6, 134.0, 132.9, 112.7, 40.6, 38.0, 22.1, 20.3, 4.9, –1.2.

4-(2-Propenyloxy)-butanoic acid (5)

To a solution of 1,4-butanediol (54.0 g, 600 mmol) in dry DMF (400 mL) was added 60% NaH (5.76 g, 240 mmol) portionwise while the solution was stirred in an ice-water bath. After the addition of NaH, the reaction flask was removed from the bath. The mixture was stirred at room temperature for 30 min and cooled in the ice-water bath again. Allyl bromide (17.3 mL, 200 mmol) was added dropwise, and the mixture stirred for 1 h. The reaction was quenched with water (500 mL) and extracted with EtOAc. The organic phase was concentrated on a rotatory evaporator, and the residue dissolved in acetone (400 mL). The solution was cooled in the ice bath and Jones reagent (prepared from 133.6 g of CrO_3, 115 mL of H_2SO_4, and 350 mL of H_2O) was added dropwise with stirring until a red color persisted (approximately 70 mL of Jones reagent was used). Volatile solvents were removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$ solution (300 mL × 2), and the organic layer was discarded. The aqueous phase was acidified by addition of 6 mol/L HCl until pH ≤ 4, and extracted with ether (100 mL × 3). The combined organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the product was obtained as a colorless liquid (19.9 g, 69%). NMR and IR data were consistent with those published in literature (19).

(4*R*)-Methyl-(5*S*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one and (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Oxalyl chloride (30 mL, 343.34 mmol) was added to a solution of acid **5** (16.5 g, 114.45 mmol) in hexane (220 mL) and the mixture was stirred at room temperature for 3 h. Volatile compounds were removed under reduced pressure, and the crude product was used in the next step without further purification. A solution of (4*R*)-methyl-(5*S*)-phenyl-oxazolidin-2-one or (4*S*)-methyl-(5*R*)-phenyl-oxazolidin-2-one (16.89 g, 95.31 mmol) in dried THF (320 mL) was cooled to –78 °C and 2.2 mol/L n-BuLi (43.3 mL, 95.31 mmol) was added dropwise. After the addition of n-BuLi, 4-(2-propenyloxy)butanoyl chloride (18.6 g, 114.38 mmol) was added in one portion. The reaction flask was moved into an ice-water bath and stirred for 30 min. The reaction was quenched with 1 mol/L K_2CO_3 (200 mL) and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1) on silica gel.

(4R)-Methyl-(5S)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +41.72 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2932 (m), 2860 (m), 1783 (s), 1702 (s), 1455 (m), 1349 (s), 1198 (s), 1120 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.29 (m, 5H), 5.98–5.85 (m, 1H), 5.66 (d, J = 7.30 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.17 (dq, J = 10.4, 1.5 Hz, 1H), 4.76 (quint, J = 6.8 Hz, 1H), 3.97 (dm, J = 5.5 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 3.14–2.97 (m, 2H), 1.99 (sept, J = 7.1 Hz, 2H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 153.0, 134.8, 133.3, 128.7, 128.6, 125.6, 116.8, 78.9, 71.7, 69.1, 54.7, 32.5, 24.4, 14.5. Anal. calcd. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98; found: C 67.55, H 6.81.

(4S)-Methyl-(5R)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one

Yield: 95%, colorless oil. $[\alpha]^{20}_D$ –40.00 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3074 (w), 2935 (m), 2861 (m), 1784 (s), 1708 (s), 1350 (s), 1198 (s), 1120 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.29 (m, 5H), 5.98–5.85 (m, 1H), 5.66 (d, J = 7.30 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.17 (dq, J = 10.4, 1.5 Hz, 1H), 4.76 (quint, J = 6.8 Hz, 1H), 3.97 (dm, J = 5.5 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 3.14–2.97 (m, 2H), 1.99 (sept, J = 7.1 Hz, 2H), 0.89 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 153.0, 134.9, 133.3, 128.7, 128.6, 125.6, 116.7, 78.9, 71.7, 69.1, 54.7, 32.5, 24.4, 14.5. Anal. calcd. for $C_{17}H_{21}NO_4$: C 67.31, H 6.98; found: C 67.42, H 6.79.

(4*R*)-Methyl-(5*S*)-phenyl-3-(4-propenyloxy-2(*R*)-methyl-butanoyl)-oxazolidine-2-one (6b) and (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy-(2*S*)-methyl-butanoyl)-oxazolidine-2-one (6c)

To a flame-dried, 1 L, round-bottomed flask was placed 27.1 g (89.33 mmol) of (4*R*)-methyl-(5*S*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one or (4*S*)-methyl-(5*R*)-phenyl-3-(4-propenyloxy)butanoyl-oxazolidin-2-one and freshly distilled THF (350 mL). The solution was cooled to –78 °C, and 2.0 mol/L NaHMDS in THF (53.6 mL, 107.2 mmol) was added dropwise over 20 min. The mixture was stirred at –78 °C for 30 min and MeI (38.0 mL, 268.0 mmol) was added. After stirring at –78 °C for an additional 4 h, the reaction was quenched with half-saturated NH_4Cl solution (300 mL). The organic phase was separated, and the aqueous

phase was extracted with EtOAc (200 mL × 3). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1) on silica gel.

6b

Yield: 84%, colorless oil. $[\alpha]^{20}_D$ +9.59 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2980 (m), 2937 (m), 2872 (m), 1782 (s), 1700 (s), 1457 (m), 1347 (s), 1242 (s), 1197 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.29 (m, 5H), 5.99–5.84 (m, 1H), 5.63 (d, *J* = 7.1 Hz, 1H), 5.28 (dq, *J* = 1.7, 17.2 Hz, 1H), 5.17 (dq, *J* = 1.7, 8.9 Hz, 1H), 4.74 (quint, *J* = 6.9 Hz, 1H), 3.95–3.89 (m, 3H), 3.53–3.48 (m, 2H), 2.18–2.03 (m, 1H), 1.79–1.67 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 152.6, 134.8, 133.4, 128.5, 125.5, 116.3, 78.6, 71.5, 68.1, 54.7, 35.1, 33.4, 17.5, 14.4. Anal. calcd. for $C_{18}H_{23}NO_4$: C 68.12, H 7.30; found: C 68.28, H 7.16.

6c

Yield: 81%, colorless oil. $[\alpha]^{20}_D$ –9.44 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2980 (m), 2932 (m), 2871 (m), 1784 (s), 1698 (s), 1459 (m), 1342 (s), 1244 (m), 1196 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 7.45–7.27 (m, 5H), 5.99–5.84 (m, 1H), 5.63 (d, *J* = 7.1 Hz, 1H), 5.28 (dq, *J* = 1.7, 17.2 Hz, 1H), 5.17 (dq, *J* = 1.7, 10.4 Hz, 1H), 4.74 (quint, *J* = 6.7 Hz, 1H), 3.95–3.87 (m, 3H), 3.53–3.46 (m, 2H), 2.18–2.04 (m, 1H), 1.79–1.67 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 176.7, 152.7, 134.9, 133.5, 128.6, 125.6, 116.5, 78.7, 71.6, 68.2, 54.8, 35.2, 33.5, 17.6, 14.5. Anal. calcd. for $C_{18}H_{23}NO_4$: C 68.12, H 7.30; found: C 67.81, H 7.51.

4-Allyloxy-(2*R*)-methyl-butan-1-ol (7b) and 4-allyloxy-(2*S*)-methyl-butan-1-ol (7c)

To a cooled solution (0 °C) **6b** or **6c** (25.27 g, 79.61 mmol) in diethyl ether (320 mL) was added 6.05 g (159.23 mmol) of $LiAlH_4$ portionwise over 40 min and stirred for 2 h. The reaction was quenched by a slow addition of water and 1 N NaOH (20 mL). The mixture was filtered, and the white precipitate was washed with ether (300 mL × 2). The combined ether solution was concentrated, and crude product was purified by vacuum distillation (bp = 60–65 °C, 0.1 mmHg).

7b

Yield: 92%, colorless oil. $[\alpha]^{20}_D$ +14.16 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3397 (s), 3081 (w), 2930 (s), 2870 (s), 1458 (m), 1097 (s), 1044 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.99–5.83 (m, 1H), 5.27 (dq, *J* = 1.6, 17.3 Hz, 1H), 5.18 (dq, *J* = 1.2, 10.4 Hz, 1H), 3.98 (d, *J* = 5.6 Hz, 2H), 3.60–3.40 (m, 4H), 2.87 (br t, *J* = 5.7 Hz, 1H), 1.83–1.50 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4, 117.1, 71.8, 68.6, 68.0, 34.1, 34.0, 17.1. Anal. calcd. for $C_8H_{16}O_2$: C 66.63, H 11.18; found: C 66.73, H 11.31.

7c

Yield: 88%, colorless oil. $[\alpha]^{20}_D$ –12.53 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3413 (s), 2957 (s), 2926 (s), 2870 (s), 1459 (m), 1099 (s), 1047 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 5.99–5.83 (m, 1H), 5.27 (dq, *J* = 1.6, 17.3 Hz, 1H), 5.18 (dq, *J* = 1.2, 10.4 Hz, 1H), 3.98 (d, *J* = 5.6 Hz, 2H), 3.60–3.40 (m, 4H), 2.87 (br t, *J* = 5.7 Hz, 1H), 1.83–1.50 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4, 117.1, 71.8, 68.6, 68.0, 34.1, 34.0, 17.1. Anal. calcd. for $C_8H_{16}O_2$: C 66.63, H 11.18; found: C 66.73, H 11.28.

Synthesis of 6-allyloxy-(4*R*)-methyl-hex-2-enoic acid methyl ester and 6-allyloxy-(4*S*)-methyl-hex-2-enoic acid methyl ester

DMSO (9.4 mL, 132.41 mmol) was added to a cooled solution (–78 °C) of oxalyl chloride (5.8 mL, 66.20 mmol) in methylene chloride (460 mL). After 5 min, a solution of **7b** or **7c** (6.80 g, 47.29 mmol) in 10 mL of methylene chloride was added. The mixture was stirred for 30 min at –78 °C, and triethylamine (29.0 mL, 208.08 mmol) was added. After stirring for an additional 1 h at –30 °C, the reaction was quenched and washed with water (200 mL × 2). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was dissolved in 1,2-dichloroethane (50 mL), $Ph_2PCHCOOMe$ (16.56 g, 47.26 mmol) was added, and it was refluxed for 6 h. Volatile solvents were removed under reduced pressure, and the crude product was purified by flash chromatography (hexane–EtOAc, 4:1) on silica gel.

6-Allyloxy-(4R)-methyl-hex-2-enoic acid methyl ester

Yield: 88%, colorless oil. $[\alpha]^{20}_D$ –43.85 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2867 (s), 1726 (s), 1658 (m), 1436 (m), 1273 (s), 1180 (m), 1103 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.95–5.82 (m, 1H), 5.80 (dd, *J* = 1.0, 15.8 Hz, 1H), 5.26 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.16 (dq, *J* = 1.6, 9.9 Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H), 3.45–3.39 (m, 2H), 2.52 (sept, *J* = 7.0 Hz, 1H), 1.65 (q, *J* = 6.7 Hz, 2H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 154.0, 134.7, 119.5, 116.7, 71.7, 67.7, 51.3, 35.7, 33.3, 19.3. Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.47, H 8.98.

6-Allyloxy-(4S)-methyl-hex-2-enoic acid methyl ester

Yield: 85%, colorless oil. $[\alpha]^{20}_D$ +45.35 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2957 (m), 2873 (m), 1730 (s), 1660 (m), 1435 (m), 1274 (m), 1183 (m), 1104 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.95–5.82 (m, 1H), 5.80 (dd, *J* = 1.0, 15.8 Hz, 1H), 5.26 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.16 (dq, *J* = 1.6, 9.9 Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H), 3.45–3.39 (m, 2H), 2.52 (sept, *J* = 7.0 Hz, 1H), 1.65 (q, *J* = 6.7 Hz, 2H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 154.0, 134.7, 119.5, 116.7, 71.7, 67.7, 51.3, 35.7, 33.3, 19.3. Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.81, H 9.36.

6-Hydroxy-(4*R*)-methyl-hex-2-enoic acid methyl ester (1b) and 6-hydroxy-(4*R*)-methyl-hex-2-enoic acid methyl ester (1c)

To a solution of 6-allyloxy-(4*R*)-methyl-hex-2-enoic acid methyl ester or 6-allyloxy-(4*S*)-methyl-hex-2-enoic acid methyl ester (8.25 g, 41.60 mmol) in anhydrous methanol (150 mL) was added 10% Pd–C (4.16 g) and *p*-toluenesulfonic acid (2.08 g). The mixture was stirred and heated under a reflux condition for 24 h, then filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 2:1).

1b

$[\alpha]^{20}_D$ –40.73 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3437 (m), 2958 (s), 2879 (m), 1725 (s), 1657 (s), 1437 (m), 1275 (s), 1210 (s), 1175 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.83 (dd, *J* = 1.0, 15.7 Hz, 1H), 3.73 (s, 3H), 3.68–3.61 (m, 2H), 2.53 (m, 1H), 2.24 (s, 1H), 1.064 (q, *J* = 6.78 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2, 154.1, 119.5, 60.2, 51.4, 38.5, 33.0, 19.3. Anal. calcd. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.91, H 8.77.

1c

$[\alpha]^{20}_D$ +44.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3429 (s), 2956 (s), 2879 (s), 1726 (s), 1658 (s), 1439 (s), 1276 (s), 1210 (s), 1175 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.88 (dd, *J* = 8.0, 15.7 Hz, 1H), 5.83 (dd, *J* = 1.0, 15.7 Hz, 1H), 3.73 (s, 3H), 3.68–3.61 (m, 2H), 2.53 (m, 1H), 2.24 (s, 1H), 1.064 (q, *J* = 6.78 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 167.2, 154.1, 119.6, 60.4, 51.4, 38.6, 33.1, 19.3. Anal. calcd. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.60, H 8.96.

General procedure for the alkylation of ketoester 8: synthesis of 9 and 10

To a solution of **8** (5 mmol) in acetone (25 mL) was added alkyl iodide **3a** or **3b** (2.5 mmol) and K_2CO_3 (7.5 mmol). The mixture was heated under a reflux condition under N_2 for 12 h. After the mixture was cooled to room temperature, water (30 mL) was added and the mixture was extracted with Et_2O (30 mL × 3). Combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane–ether, 20:1).

9

Yield: 86%, colorless oil. IR (neat, cm^{-1}): 3079 (w), 2956 (s), 2896 (s), 1751 (s), 1730 (s), 1436 (m), 1251 (m), 1159 (m), 855 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.06 (d, *J* = 15.6 Hz, 1H), 5.54 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.78 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 3.71 (s, 3H), 2.57–1.86 (m, 8H), 1.68 (s, 2H), 1.64–1.32 (m, 4H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.7, 171.5, 143.7, 133.7, 128.6, 112.0, 60.4, 52.5, 37.9, 33.6, 32.9, 32.8, 24.7, 22.1, 19.6, –1.2. Anal. calcd. for $C_{18}H_{30}O_3Si$: C 67.03, H 9.38; found: C 66.88, H 9.12.

10

Yield: 88%, colorless oil. IR (neat, cm^{-1}): 3080 (w), 2957 (s), 2928 (s), 1754 (s), 1729 (s), 1600 (m), 1460 (m), 1250 (s), 1157 (m), 856 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.05 and 6.01 (d, *J* = 15.7 and 15.7 Hz, 1H), 5.44–5.32 (m, 1H), 4.79 (d, *J* = 2.0 Hz, 1H), 4.66 (d, *J* = 2.0 Hz, 1H), 3.70 and 3.69 (s, 3H), 2.63–1.77 (m, 8H), 1.68 (s, 2H), 1.67–1.12 (m, 3H), 1.00 and 0.99 (d, *J* = 6.7 and 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.71, 214.65, 171.6, 171.4, 143.74, 143.69, 135.5, 132.1, 132.0, 112.13, 112.08, 60.4, 60.3, 52.4, 38.0, 37.8, 37.5, 37.4, 32.9, 32.7, 32.0, 31.9, 31.8, 22.1, 22.0, 20.8, 20.7, 19.5, –1.2. HR-MS (EI) calcd. for $C_{19}H_{31}O_3Si$ (M^+): 336.2121; found: 336.2121.

General procedure for the alkylation of ketoester 13: synthesis of 14–16

To a flame-dried, 50 mL, round-bottomed flask equipped with a magnetic bar was placed 0.65 g (17 mmol) of 60% NaH in mineral oil and 27 mL of freshly distilled THF. The mixture was stirred in an ice bath, and a solution of **13** (15 mmol) in 3 mL of THF was added slowly. The mixture was stirred for 5 min, and 2.5 mol/L solution of *n*-BuLi (15 mmol) was added. After stirring for an additional 5 min, a solution of alkyl iodide **3a**, **3b**, or **3c** (10 mmol) in 3 mL of THF was added into the orange-yellow solution. The mixture was stirred and allowed to warm to room temperature overnight. The reaction was quenched with water (25 mL) and extracted with ether (30 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated with a rotatory evaporator. The crude product was purified by column chromatography (silica gel, pentane–ether, 20:1) to give a mixture of diastereomers.

14

Yield: 67%, yellow oil. $[\alpha]^{20}_D$ +49.70 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3083 (w), 2957 (s), 2967 (s), 1753 (s), 1730 (s), 1436 (m), 1250 (m), 857 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.05 (d, *J* = 15.6 Hz, 1H), 5.55 (dt, *J* = 7.0, 15.6 Hz, 1H), 4.78 (d, *J* = 2.2 Hz, 1H), 4.66 (s, 1H), 3.75 and 3.74 (s, 3H), 2.86 and 2.74 (d, *J* = 10.0 and 11.44 Hz, 1H), 2.70–2.40 (m, 1H), 2.39–2.21 (m, 1H), 2.14–2.07 (m, 2H), 2.03–1.74 (m, 1H), 1.72–1.59 (m, 1H), 1.68 (s, 2H), 1.50–1.34 (m, 4H), 1.18 and 1.16 (d, *J* = 6.34 and 6.45 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 212.5, 169.63, 169.59, 143.8, 133.6, 129.8, 111.9, 111.2, 62.9, 62.8, 52.3, 50.5, 47.9, 36.2, 35.0, 34.1, 33.6, 32.6, 32.5, 30.4, 29.3, 27.8, 27.4, 27.3, 22.1, 19.7, 19.1, 15.8, –1.2. Anal. calcd. for $C_{19}H_{32}O_3Si$: C 67.81, H 9.58; found: C 67.66, H 9.52.

15

Yield: 70%, yellow oil. $[\alpha]^{20}_D$ +37.22 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2955 (s), 2874 (m), 1756 (s), 1731 (s), 1250 (m), 853 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 6.02 (d, *J* = 15.7 Hz, 1H), 5.47–5.35 (m, 1H), 4.78 (d, *J* = 1.7 Hz, 1H), 4.66 (s, 1H), 3.75 and 3.74 (s, 3H), 2.95 and 2.85 (d, *J* = 10.3 and 9.5 Hz, 1H), 2.75–2.42 (m, 1H), 2.35–2.13 (m, 2H), 1.99–1.59 (m, 2H), 1.68 (s, 2H), 1.39–1.23 (m, 3H), 1.18–1.06 (m, 4H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 212.6, 169.6, 169.6, 143.8, 143.8, 135.9, 135.8, 131.9, 131.8, 112.1, 112.0, 63.0, 62.8, 52.3, 50.5, 48.2, 37.2, 37.1, 36.2, 35.1, 35.1, 34.6, 34.1, 33.6, 28.8, 27.5, 22.1, 22.1, 20.9, 20.5, 19.2, –1.2. Anal. calcd. for $C_{20}H_{34}O_3Si$: C 68.52, H 9.78; found: C 68.70, H 9.85.

16

Yield: 79%, yellow oil. $[\alpha]^{20}_D$ +45.50 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3084 (w), 2956 (s), 2867 (s), 1759 (s), 1729 (s), 1444 (m), 1250 (s), 1158 (m), 849 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.97 (d, *J* = 15.7 Hz, 1H), 5.42–5.30 (m, 1H), 4.74 (d, *J* = 2.0 Hz, 1H), 4.61 (br s, 2H), 3.70 and 3.69 (s, 3H), 2.81 and 2.69 (d, *J* = 9.6 and 11.6 Hz, 1H), 2.65–2.10 (m, 4H), 1.97–1.53 (m, 2H), 1.64 (s, 2H), 1.40–1.19 (m, 3H), 1.12 and 1.11 (d, *J* = 6.3 and 6.4 Hz, 3H),

1.05–1.00 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), –0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.3, 212.3, 169.5, 169.4, 143.6, 143.5, 135.7, 135.6, 131.8, 131.7, 111.93, 111.87, 62.8, 62.7, 52.1, 50.5, 47.8, 37.1, 36.8, 36.1, 35.0, 34.7, 34.6, 34.0, 33.4, 28.4, 27.6, 21.98, 21.96, 20.7, 20.5, 19.6, 19.0, –1.3. HR-MS (EI) calcd. for $C_{20}H_{34}O_3Si$ (M^+): 350.2277; found: 350.2241.

General procedure for decarbomethoxylation: synthesis of 11–12 and 17–19

To a solution of β-keto ester (3.0 mmol) in DMSO (6.0 mL) was added potassium cyanide (6.0 mmol) and water (6.0 mmol). The mixture was heated under reflux for 30 min, allowed to cool to room temperature, diluted with water (20 mL), and extracted with ether (20 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, pentane–ether, 20:1).

11

Yield: 66%, colorless oil. IR (neat, cm^{-1}): 3079 (w), 2956 (s), 1740 (s), 1250 (s), 1157 (m), 856 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.06 (d, *J* = 15.6 Hz, 1H), 5.57 (dt, *J* = 7.06, 15.6 Hz, 1H), 4.78 (d, *J* = 2.01, 1H), 4.66 (s, 1H), 2.36–1.93 (m, 7H), 1.88–1.72 (m, 2H), 1.69 (s, 2H), 1.62–1.21 (m, 4H), 0.39 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 143.8, 133.5, 130.1, 111.8, 49.1, 38.1, 32.8, 29.6, 29.4, 27.5, 22.2, 20.7, –1.2. Anal. calcd. for $C_{16}H_{28}OSi$: C 72.66, H 10.67; found: C 72.50, H 10.49.

12

Yield: 83%, colorless oil. $[\alpha]^{20}_D$ –10.13 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3080 (w), 2956 (s), 2870 (s), 1738 (s), 1249 (s), 1160 (m), 857 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.02 (d, *J* = 15.7 Hz, 1H), 5.48–5.36 (m, 1H), 4.79 (d, *J* = 2.2 Hz, 1H), 4.66 (br s, 1H), 2.35–1.93 (m, 6H), 1.87–1.65 (m, 2H), 1.69 (s, 2H), 1.60–1.15 (m, 4H), 1.02 and 1.01 (d, *J* = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 143.9, 143.8, 136.1, 136.0, 131.8, 131.6, 111.94, 111.89, 49.3, 49.1, 38.14, 38.11, 37.4, 37.1, 35.2, 34.8, 29.63, 29.59, 27.8, 27.5, 22.14, 22.12, 20.9, 20.7. 20.5, –1.2. HR-MS (EI) calcd. for $C_{17}H_{30}OSi$ (M^+): 278.2066; found: 278.2079.

17

Yield: 78%, colorless oil. $[\alpha]^{20}_D$ +71.31 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3081 (w), 2954 (s), 2862 (s), 1743 (s), 1459 (w), 1250 (s), 1158 (m), 857 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.06 (d, *J* = 15.3 Hz, 1H), 5.63–5.54 (m, 1H), 4.78 (d, *J* = 2.2 Hz, 1H), 4.66 (s, 1H), 2.52–2.03 (m, 6H), 1.97–1.62 (m, 2H), 1.69 (s, 2H), 1.51–1.20 (m, 3H), 1.18–1.05 (m, 1H), 1.14 and 1.09 (d, *J* = 6.4 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.6, 220.7, 143.8, 133.5, 133.4, 130.1, 130.1, 111.8, 50.8, 47.0, 46.8, 46.4, 35.6, 36.9, 32.8, 32.7, 30.2, 29.7, 29.4, 28.3, 27.5, 22.2, 20.8, 20.3, –1.2. Anal. calcd. for $C_{17}H_{30}OSi$: C 73.31, H 10.86; found: C 73.41, H 10.68.

18

Yield: 94%, colorless oil. $[\alpha]^{20}_D$ +41.65 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3079 (w), 2955 (s), 2870 (s), 1740 (s), 1593 (m), 1458 (m), 1249 (s), 1158 (m), 968 (m), 854 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.02 (d, *J* = 15.6 Hz, 1H), 5.50–5.35 (m, 1H), 4.79 (d, *J* = 2.0 Hz, 1H), 4.66 (s, 1H), 2.50–2.05 (m, 4H), 1.95–1.60 (m, 2H), 1.69 (s, 2H), 1.40–1.18 (m, 5H), 1.13 and 1.09 (d, *J* = 6.4 and 6.5 Hz, 3H), 1.01 and 1.00 (d, *J* = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 221.7, 220.7, 143.9, 143.8, 136.2, 136.0, 131.8, 131.6, 112.0, 111.9, 50.9, 47.3, 46.9, 46.4, 38.5, 37.4, 37.1, 36.9, 35.2, 34.8, 29.7, 28.6, 28.3, 27.4, 22.2, 22.1, 20.9, 20.8, 20.5, 20.3, –1.2. Anal. calcd. for $C_{18}H_{32}OSi$: C 73.90, H 11.03; found: C 73.85, H 10.95.

19

Yield: 74%, colorless oil. $[\alpha]^{20}_D$ +66.45 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3081 (w), 2956 (s), 2923 (s), 2865 (m), 1744 (s), 1250 (s), 1158 (m), 850 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.02 (d, *J* = 15.7 Hz, 1H), 5.47–5.36 (m, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 4.65 (d, *J* = 1.4 Hz, 1H), 2.50–2.06 (m, 5H), 1.91–1.62 (m, 3H), 1.69 (s, 2H), 1.43–1.21 (m, 2H), 1.13 and 1.08 (d, *J* = 6.4 and 6.6 Hz, 3H), 1.17–1.06 (m, 1H), 1.02 and 1.00 (d, *J* = 6.7 and 6.7 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 221.6, 220.6, 143.8, 136.1, 136.0, 131.8, 131.7, 111.9, 51.0, 47.0, 46.8, 46.4, 38.6, 37.4, 37.1, 37.0, 35.1, 34.8, 29.7, 28.4, 28.3, 27.8, 22.1, 20.84, 20.76, 20.6, 20.3, –1.2. HR-MS (EI) calcd. for $C_{18}H_{32}OSi$ (M^+): 292.2222; found: 292.2241.

α-Chlorination of cyclopentanone, intramolecular [4 + 3] cycloaddition, and desilylation of allylsilane: synthesis of 20

To a cooled solution (–78 °C) of ketone **18** (2.0 mmol) in THF (15 mL) was slowly added a solution of LDA (prepared by adding a 2.5 mol/L solution of *n*-BuLi (2.5 mmol) into a solution of diisopropylamine (3.0 mmol) in THF (5 mL) at 0 °C). The mixture was stirred at –78 °C for 30 min and trifluoromethanesulfonyl chloride (2.5 mmol) was added dropwise. After stirring for 5 min, the reaction was quenched with water (20 mL) and extracted with ether (15 mL × 3). The combined organic phases were washed with water (20 mL), dried over magnesium sulfate, filtered, and concentrated. Volatile solvents were removed under high vacuum. The resulting colorless oil was dissolved in freshly distilled ether (10 mL), cooled to –78 °C, and diluted with trifluoroethanol (10 mL). The mixture was stirred for a few minutes and triethylamine (6.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature overnight, quenched with water (20 mL), and extracted with ether (15 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was dried under high vacuum. The resulting yellow oil was dissolved in methylene chloride (20 mL), and $TsOH{\cdot}H_2O$ (0.2 mmol) was added. The mixture was stirred at room temperature for 6 h and washed with water (20 mL). The organic phase was separated and dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using hexane–EtOAc (30:1) as the eluent. Ketone **20** was obtained as a colorless oil in 74% yield. $[\alpha]^{20}_D$ +44.60 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3073 (w), 2952 (s), 2867 (s), 1735 (s), 1643 (w), 1455 (m), 1154 (w). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.83 (d, *J* = 13.5 Hz, 2H), 2.46–1.68 (m, 8H), 1.58–0.92 (m,

6H), 1.04 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.8, 146.5, 115.0, 61.1, 58.6, 52.7, 46.9, 43.2, 39.9, 39.4, 35.1, 31.7, 28.0, 21.0, 18.3. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.25, H 10.20.

Simmons–Smith cyclopropanation: synthesis of 22

To a cooled solution (0 °C) of **20** (2.29 mmol) in methylene chloride (5 mL) was added methylene iodide (5.4 mL, 5.8 mmol) and 1.0 mol/L solution of diethylzinc in hexane (23 mL, 23 mmol). The mixture was stirred vigorously for 12 h while it was allowed to warm to room temperature. The reaction was quenched with water (20 mL), 1 N HCl (5 mL) was added, and it was extracted with ether (20 mL × 3). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated using a rotatory evaporator. The crude product was purified by flash chromatography (3:1, hexane–CH_2Cl_2). Ketone **22** was obtained in 95% yield as a colorless oil. $[\alpha]^{20}_D$ +12.63 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2869 (s), 1728 (s), 1457 (m), 1390 (m), 1164 (m), 1114 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.63–2.51 (m, 1H), 2.28–2.11 (m, 3H), 1.99–1.94 (m, 4H), 1.84–1.77 (m, 1H), 1.56–1.43 (m, 1H), 1.36–1.13 (m, 5H), 1.03 (d, J = 6.88 Hz, 3H), 0.99–0.95 (m, 1H), 0.91 (d, J = 5.33 Hz, 3H), 0.83–0.75 (m, 1H), 0.51–0.39 (m, 2H), 0.31–0.15 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.1, 61.6, 55.0, 41.2, 42.8, 39.1, 35.1, 31.6, 27.3, 21.1, 18.4, 17.0, 14.7, 12.3. Anal. calcd. for $C_{16}H_{24}O$: C 80.70, H 10.41; found: C 82.60, H 10.30.

Baeyer–Villiger oxidation: synthesis of 23 and 24

To a solution of ketone **22** (2.15 mmol) in DMF (4 mL) was added MMPP (10.63 g, 21.50 mmol), and the resulted suspension was stirred at room temperature for 24 h. The mixture was diluted with water (20 mL) and extracted with ether (20 mL × 3). The combined ether solutions were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1).

23

Yield: 68%, white solid (recrystallized from hexane–EtOAc), mp 52–54 °C. $[\alpha]^{20}_D$ +26.46 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2956 (d), 2869 (d), 1728 (d), 1457 (m), 1390 (m), 1164 (m), 1114 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.36–4.31 (m, 1H), 2.70–2.46 (m, 3H), 2.03 (dd, J = 7.4, 13.5 Hz, 1H), 1.94–1.83 (m, 1H), 1.78–1.65 (m, 2H), 1.61–1.33 (m, 3H), 1.25–1.03 (m, 2H), 1.10 (d, J = 6.9 Hz, 3 H), 0.92 (br s, 1H), 0.88 (d, J = 6.0 Hz, 3H), 0.53–0.42 (m, 2H), 0.38–0.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.3, 85.4, 57.7, 51.1, 44.5, 42.0, 41.4, 38.0, 36.0, 33.0, 26.6, 22.2, 18.0, 16.7, 14.9, 14.7. Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.23, H 9.89.

24

Yield: 16%, white solid (recrystallized from hexane–EtOAc), mp 65–67 °C. $[\alpha]^{20}_D$ –103.65 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2956 (s), 2917 (s), 2871 (s), 1722 (s), 1452 (w), 1374 (w), 1266 (w), 1098 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.66–2.38 (m, 3H), 2.21–1.79 (m, 5H), 1.67–1.53 (m, 2H), 1.39–1.21 (m, 2H), 1.13–0.96 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.79–0.73 (m, 1H), 0.55–0.28 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 178.0, 90.6, 56.8, 46.8, 43.5, 42.6, 41.7, 41.1, 35.6, 32.1, 25.4, 23.0, 18.6, 17.5, 15.1, 14.3. Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.50, H 9.71.

Hydrogenolysis of a cyclopropane: synthesis of 25

To a 20 mL hydrogenation vessel was placed 0.90 mmol of cyclopropane **23**, 9.0 mL of glacial acetic acid, PtO_2 (4 equiv.), and NaOAc (4 equiv.). The vessel was connected to a hydrogenation apparatus, and the system was flushed with H_2 gas for a few minutes. The hydrogen pressure was adjusted to 100 psi (1 psi = 6.894 757 kPa), and the mixture was stirred under hydrogen for 12 h. The vessel was vented, and the catalyst was filtered off. The filtrate was partitioned between ether (20 mL) and water (20 mL). The organic phase was separated, and the aqueous phase was extracted with ether (20 mL × 2). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1). Lactone **25** was synthesized in 98% yield as a white crystalline solid. mp 91 to 92 °C. $[\alpha]^{20}_D$ +15.23 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 2955 (s), 2872 (s), 1720 (s), 1455 (m), 1113 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.36 (q, J = 3.5 Hz, 1H), 2.73–2.60 (m, 1H), 2.43–2.34 (m, 1H), 2.07 (dd, J = 8.3, 13.8 Hz, 1H), 1.93–1.82 (m, 2H), 1.75–1.16 (m, 8H), 1.12 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.98–0.96 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.3, 85.3, 54.0, 51.3, 46.3, 43.0, 42.6, 42.0, 36.5, 36.4, 32.9, 32.5, 29.5, 27.3, 23.2, 18.3. Anal. calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.80, H 10.56.

Hydrolysis of lactone 25 and esterification of carboxylic acid 31: synthesis of 32

To a 10 mL round-bottomed flask equipped with a reflux condenser was placed **25** (0.05 g, 0.20 mmol), MeOH (2.0 mL), water (1.0 mL), and KOH (0.5 g). The mixture was heated and stirred under a reflux condition for 12 h. The mixture was allowed to cool to room temperature, was diluted with 2 N HCl (5 mL), and extracted with ether (10 mL × 3). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was dissolved in 5 mL of ether; a solution of diazomethane in ether was added until a yellow color persisted. The mixture was stirred for 5 min, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1). Ester **32** was obtained as a colorless oil (0.053 g, 95%). $[\alpha]^{20}_D$ –27.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3424 (m), 2960 (s), 2872 (s), 1720 (s), 1466 (m), 1175 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80–3.74 (m, 1H), 3.67 (s, 3H), 2.26 (dd, J = 9.3, 15.0 Hz, 1H), 2.04–1.83 (m, 4H), 1.73–1.35 (m, 6H), 1.26–1.15 (m, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.96–0.93 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.6, 72.4, 55.4, 51.4, 49.7, 46.9, 41.4, 39.4, 37.7, 36.8, 35.9, 32.0, 31.9, 31.2, 24.1, 20.2, 19.3. Anal. calcd. for $C_{17}H_{30}O_3$: C 72.30, H 10.71; found: C 72.42, H 10.61.

Dehydration of alcohol 32 using Tf_2O–pyridine: synthesis of 35

To a solution of **32** (0.01 g, 0.04 mmol) in pyridine (1.0 mL) was added Tf_2O (0.013 mL, 0.08 mmol), and it

was stirred for 12 h at room temperature. The mixture was diluted with water (5 mL) and extracted with ether (5 mL × 3). Combined organic phases were washed with 0.5 N HCl (5 mL) and brine, dried over magnesium sulfate, filtered, and concentrated. After a chromatographic purification (silica gel, hexane–EtOAc, 10:1), **35** was obtained in 90% yield as a colorless oil. $[\alpha]^{20}_D$ +94.86 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2949 (s), 2918 (s), 1730 (s), 1467 (m), 1220 (m), 1158 (s). ^1H NMR (250 MHz, $CDCl_3$) δ: 3.59 (s, 3H), 2.50–2.30 (m, 1H), 2.25–1.59 (m, 8H), 1.65 (s, 3H), 1.44–1.35 (m, 2H), 1.20–1.10 (m, 2H), 0.97 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 177.3, 136.9, 134.7, 61.7, 51.5, 38.1, 36.4, 35.7, 35.1, 34.43, 34.35, 29.6, 27.6, 26.2, 25.7, 22.1, 16.3. Anal. calcd. for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found: C 77.34, H 10.44.

Dehydration of alcohol 32 using $POCl_3$–HMPA–pyridine and hydrolysis of ester: synthesis of 36

A 10 mL round-bottomed flask was charged with 0.053 g (0.19 mmol) of **32**, 2.0 mL of HMPA, and 0.2 mL of $POCl_3$. The resulting white suspension was stirred for 1 h at room temperature and for another 1 h in an oil bath at 50 °C. Pyridine (0.2 mL) was added, and the mixture was stirred at 50 °C for 1 h, at 75 °C for 45 min, and at 100 °C for 30 min. The mixture was allowed to cool to room temperature and was quenched by the dropwise addition of water (2 mL). The mixture was extracted with ether (5 mL × 3). The combined organic phases were washed with water (5 mL), dried over magnesium sulfate, filtered, and concentrated. The volatile compounds were removed under high vacuum, and the residue was dissolved in DMSO (2 mL). A few drops of water and 0.1 g of KOH were added, and the mixture was heated under reflux for 1 h. The reaction was allowed to cool to room temperature, 2 N HCl (5 mL) was added, and the mixture was extracted with ether (10 mL × 3). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 10:1). Acid **36** was obtained as a white solid (0.04 g, 88%). mp 133–135 °C. $[\alpha]^{20}_D$ +17.78 (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): 3435–2372 (s), 2952 (s), 1697 (s), 1466 (m), 1249 (m), 1205 (s). ^1H NMR (300 MHz, $CDCl_3$) δ: 12.00 (br, 1H), 5.50 (t, *J* = 8.4 Hz, 1H), 2.55 (d, *J* = 13.4 Hz, 1H), 2.31 (d, *J* = 13.5 Hz, 1H), 2.15–1.81 (m, 5H), 1.77 (s, 3H), 1.72–1.60 (m, 2H), 1.25–1.10 (m, 2H), 1.02 (d, *J* = 15.0 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.5, 135.4, 125.9, 58.2, 52.0, 40.7, 39.1, 38.9, 38.2, 34.7, 29.7, 28.1, 26.4, 20.1. Anal. calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.94, H 10.40.

Carboxy inversion: synthesis of (+)-dactylol (37)

A dried, 10 mL, round-bottomed flask was charged with 0.03 g (0.11 mmol) of acid **36**, 2.0 mL of 20% solution of $COCl_2$ in toluene, and four drops of DMF. The mixture was stirred at room temperature for 1 h, and then heated under reflux for 30 min. The mixture was allowed to cool to room temperature and was diluted with pentane (5 mL), filtered, and concentrated. The resulting colorless oil was dissolved in benzene (2.0 mL). *m*-CPBA (0.019 g, 0.11 mmol), pyridine (0.1 mL, 0.12 mmol), and DMAP (0.005 g) were added. The mixture was stirred at room temperature for 24 h, filtered, and concentrated. The volatile compounds were removed under high vacuum, and the residue was dissolved in ether (2 mL). The solution was cooled in an ice-water bath and 0.013 g (0.33 mmol) of $LiAlH_4$ was added. The suspension was stirred at 0 °C for 2 h and slowly quenched with water, filtered, and the white precipitate washed thoroughly with ether (5 mL × 3). The combined organic phases were concentrated, and the crude product was purified by flash chromatography (hexane–EtOAc, 10:1). (+)-Dactylol (**37**) was obtained as a white solid (0.012 g, 50%). mp 49 to 50 °C (lit. value (15e), mp 50.3–51.5 °C). $[\alpha]^{20}_D$ +21.38 (*c* 1.0, $CHCl_3$) (lit. value (15e)) $[\alpha]^{20}_D$ +22.5). IR (neat, cm^{-1}): 3500 (w), 2955 (s), 2872 (s), 1465 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 5.49 (t, *J* = 8.4 Hz, 1H), 2.21 (d, *J* = 13.4 Hz, 1H), 2.07 (d, *J* = 13.4 Hz, 1H), 1.95–1.85 (m, 2H), 1.82 (s, 3H), 1.80–1.71 (m, 1H), 1.70–1.60 (m, 1H), 1.57–1.49 (m, 2H), 1.46 (dd, *J* = 15.0, 7.9 Hz, 1H), 1.33 (br s, 1H), 1.09–0.95 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.71 (d, *J* = 114.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9, 124.6, 82.8, 52.9, 43.1, 40.4, 39.4, 39.3, 36.5, 35.2, 29.5, 29.3, 28.9, 27.9, 19.2. Anal. calcd. for $C_{15}H_{26}O$: C 81.02, H 11.78; found: C 81.27, H 12.00.

[4 + 3] Cycloaddition of 11: synthesis of 38 and 39

Ketone **11** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadduct **38** and **39** were obtained and separated by hexane–EtOAC (20:1).

38

Yield: 47%, colorless oil. IR (neat, cm^{-1}): 3069 (m), 2950 (s), 2872 (s), 1730 (s), 1454 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.84 (s, 1H), 4.80–4.73 (m, 1H), 2.45–2.30 (m, 3H), 2.26–2.09 (m, 2H), 2.00–1.80 (m 3H), 1.79–1.40 (m, 6H), 1.39–1.29 (m, 1H), 1.21–1.09 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 146.0, 115.4, 58.2, 51.7, 43.7, 41.5, 40.0, 36.7, 36.3, 33.8, 26.3, 19.8. Anal. calcd. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.92, H 9.65.

39

Yield: 18%, colorless oil. IR (neat, cm^{-1}): 3071 (w), 2957 (s), 2870 (m), 1737 (s), 1451 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.80–4.65 (m, 2H), 2.70 (dd, *J* = 7.1, 15.0 Hz, 1H), 2.26–2.54 (m, 1H), 2.38 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.30–2.07 (m, 5H), 1.91–1.27 (m, 8H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.4, 145.8, 114.6, 58.5, 51.6, 44.8, 38.9, 36.1, 33.2, 30.0, 27.8, 26.2, 21.6. Anal. calcd. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.95, H 9.33.

[4 + 3] Cycloaddition of 12: synthesis of 45 and 46

Ketone **12** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **45** and **46** were obtained and separated by pentane–Et_2O (20:1).

45

Yield: 57%, colorless oil. $[\alpha]^{20}_D$ +41.46 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3070 (w), 2950 (s), 2863 (m), 1733 (s), 1456 (m). ^1H NMR (250 MHz, $CDCl_3$) δ: 4.87 (br s, 1H), 4.80 (t,

J = 1.9 Hz, 1H), 2.49–2.36 (m, 3H), 2.30–2.13 (m, 2H), 1.99–1.62 (m, 5H), 1.55–1.22 (m, 4H), 1.16–1.05 (m, 1H), 1.00 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.3, 145.8, 115.3, 59.1, 59.0, 43.7, 43.1, 40.3, 39.5, 37.4, 35.1, 31.9, 19.7, 18.2. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1499.

46

Yield: 9%, colorless oil. $[\alpha]^{20}_D$ –108.75 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3070 (w), 2951 (s), 2866 (m), 1733 (s), 1449 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.80–4.73 (m, 2H), 2.72 (dd, *J* = 5.9, 12.5 Hz, 1H), 2.62–2.50 (m, 1H), 2.38 (dd, *J* = 2.9, 11.5 Hz, 1H), 2.27–1.61 (m, 8H), 1.40–1.22 (m, 2H), 1.09–0.95 (m, 2H), 1.00 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.4, 145.7, 114.7, 59.3, 58.3, 44.8, 39.1, 37.1, 34.4, 31.3, 31.2, 29.2, 26.2, 18.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1517.

[4 + 3] Cycloaddition of 17: synthesis of 49–52

Ketone **17** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **49**–**52** were obtained and separated by pentane–Et_2O (20:1 to 10:1). Ketone **49** and **50** were not completely isolable. The mixture was obtained as slightly yellow oil (41%). Further chromatographic purification on silica gel (pentane–Et_2O, 30:1) afforded a sufficient amount of each isomer along with a mixture of the two isomers.

49

$[\alpha]^{20}_D$ +62.08 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2949 (s), 2866 (s), 1731 (s), 1642 (m), 1452 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.83 (s, 1H), 4.77 (t, *J* = 2.0 Hz, 1H), 2.46–2.33 (m, 2H), 2.31–2.15 (m, 2H), 2.13–2.00 (m, 2H), 1.99–1.84 (m, 2H), 1.81–1.61 (m, 3H), 1.59–1.24 (m, 3H), 1.22–1.08 (m, 1H), 1.04 (d, *J* = 66 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.8, 146.6, 115.1, 60.2, 52.7, 51.3, 46.1, 41.8, 39.2, 36.4, 33.6, 28.0, 26.3, 21.0. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1510.

50

$[\alpha]^{20}_D$ +13.64 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3069 (w), 2934 (s), 2869 (m), 1733 (s), 1643 (m), 1456 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.91–4.88 (m, 1H), 4.85 (br s, 1H), 2.64 (dd, *J* = 4.7, 12.6 Hz, 1H), 2.54 (d, *J* = 13.6 Hz, 1H), 2.38–2.12 (m, 5H), 1.99–1.41 (m, 7H), 1.28–1.17 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 223.5, 146.3, 114.2, 57.9, 55.0, 51.6, 47.3, 40.1, 36.9, 34.3, 34.2, 30.7, 25.8, 15.1. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1520.

51

Yield: 7%, colorless oil. $[\alpha]^{20}_D$ +32.17 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3072 (w), 2953 (s), 2871 (s), 1737 (s), 1637 (w), 1457 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.78–4.71 (m, 2H), 2.75–2.63 (m, 1H), 2.48–2.34 (m, 2H), 2.29–2.04 (m, 5H), 1.89–1.26 (m, 6H), 1.13 (dd, *J* = 6.7, 20.7 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.0, 145.8, 114.8, 59.8, 54.2, 51.5, 38.3, 37.5, 36.5, 34.7, 33.9, 30.1, 23.9, 21.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1503.

52

Yield: 4%, colorless oil. IR (neat, cm^{-1}): 3072 (w), 2948 (s), 2872 (s), 1738 (s), 1635 (w), 1455 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.79–4.74 (m, 2H), 2.52–1.52 (m, 13H), 1.44–1.19 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.4, 145.6, 115.3, 59.6, 52.3, 50.8, 37.5, 35.7, 34.3, 30.7, 29.9, 29.6, 21.8, 15.6. HR-MS (EI) calcd. for $C_{14}H_{20}O$ (M^+): 204.1514; found: 204.1524.

[4 + 3] Cycloaddition of 19: synthesis of 53–56

Ketone **19** was subjected to an α-chlorination, [4 + 3] cycloaddition, and desilylation conditions using the procedure described in the synthesis of ketone **20**. Cycloadducts **53**–**56** were obtained and separated by pentane–Et_2O (30:1 to 10:1).

53

Yield: 11%, colorless oil. $[\alpha]^{20}_D$ +67.40 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2927 (s), 2867 (m), 1732 (s), 1455 (m), 1379 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.85 (br s, 1H), 4.80–4.78 (m, 1H), 2.45–2.36 (m, 1H), 2.30–1.90 (m, 7H), 1.80–1.57 (m, 3H), 1.50–1.40 (m, 1H), 1.38–1.23 (m, 2H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.83 (d, *J* = 7.2Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 221.1, 147.6, 115.2, 60.8, 53.4, 52.9, 46.6, 39.5, 39.3, 37.5, 34.1, 31.7, 28.1, 21.0, 15.1. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.67, H 10.33.

54

Yield: 41%, colorless oil. $[\alpha]^{20}_D$ +34.55 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2933 (s), 2868 (m), 1731 (s), 1452 (m), 1165 (w). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.92–4.88 (m, 1H), 4.85 (br s, 1H), 2.64–2.53 (m, 2H), 2.35–2.12 (m, 5H), 1.94–1.81 (m, 2H), 1.60–1.18 (m, 5H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 223.6, 146.1, 114.2, 61.2, 58.7, 51.5, 48.0, 40.8, 28.3, 34.9, 34.8, 34.5, 30.7, 17.3, 15.1. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.36, H 9.97.

55

Yield 12%, colorless oil. $[\alpha]^{20}_D$ +75.05 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950 (s), 2932 (s), 2863 (m), 1732 (s), 1456 (m), 1375 (m). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.77 (br s, 1H), 4.75–4.72 (m, 1H), 2.71 (dd, *J* = 7.6, 14.9 Hz, 1H), 2.50–1.60 (m, 10H), 1.43–1.07 (m, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.8, 145.7, 114.8, 60.5, 58.1, 54.1, 38.7, 38.4, 37.2, 34.8, 34.6, 32.0, 31.3, 23.8, 18.6. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.39, H 10.19.

56

Yield 7%, colorless oil. $[\alpha]^{20}_D$ +25.40 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956 (s), 2868 (s), 1737 (s), 1460 (m), 1169 (m), 1121 (w). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.82–4.76 (m, 2H), 2.53–1.61 (m, 12H), 1.50–1.18 (m, 2H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 220.5, 146.0, 115.7, 59.4, 54.3, 51.3, 36.9, 35.2, 35.0, 34.4, 33.4, 31.9, 29.4, 18.4, 15.4. Anal. calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.51, H 9.99.

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References

1. (*a*) M. Harmata. Acc. Chem. Res. **34**, 595 (2001;. (*b*) M. Harmata. Tetrahedron, **53**, 6235 (1997); (*c*) M. Harmata. *In* Advances in cycloaddition. Vol. 4. *Edited by* M. Lautens. JAI, Greenwich. 1997. pp. 41–86.
2. (*a*) M. Harmata and S. Wacharasindhu. Org. Lett. **7**, 2563, (2005); (*b*) M. Harmata and G.J. Bohnert. Org. Lett. **5**, 59 (2003); (*c*) M. Harmata and P. Rashatasakhon. Org. Lett. **3**, 2533 (2001); (*d*) M. Harmata and P. Rashatasakhon. Org. Lett. **2**, 2913 (2000); (*e*) M. Harmata and K.W. Carter. Tetrahedron Lett. **38**, 7985 (1997); (*f*) J. Cha and J. Oh. Curr. Org. Chem. **2**, 217 (1998).
3. (*a*) Y. Wang, A.Yong, M. Atta, and F.G. West. J. Am. Chem. Soc. **121**, 876 (1999); (*b*) M. Harmata, S. Elomari, and C.L. Barnes. J. Am. Chem. Soc. **118**, 2860 (1996); (*c*) M. Harmata, S. Elahmad, and C.L. Barnes. J. Org. Chem. **59**, 1241 (1994); (*d*) F.G. West, C. Hartke-Karger, D.J. Koch, C.E. Kuehn, and A.M. Arif. J. Org. Chem. **58**, 6795 (1993).
4. W.H. Bunnelle and B.A. Narayanan. Org. Synth. **69**, 89 (1990).
5. R. Scheffold and E. Saladin. Angew. Chem. Int. Ed. Engl. **11**, 229 (1972).
6. S.E. Denmark and C.B.W. Senanayake. J. Org. Chem. **58**, 1853 (1993).
7. R. Boss and R. Scheffold. Angew. Chem. Int. Ed. Engl. **15**, 558 (1976).
8. (*a*) A.P. Krapcho. Synthesis, 805 (1982); (*b*) A.P. Krapcho. Synthesis, 893 (1982).
9. J.N. Marx and L.R. Norman. J. Org. Chem. **40**, 1602 (1975).
10. M. Harmata and P. Rashatasakhon. Tetrahedron Lett. **43**, 3641 (2002).
11. F.N. Tebbe, G.W. Parshall, and G.S. Reddy. J. Am. Chem. Soc. **100**, 3611 (1978).
12. B.M. Trost and L.N. Jungheim. J. Am. Chem. Soc. **102**, 7910 (1980).
13. C.M. Marson and P.R. Giles. Synthesis using Vilsmeier reagents. CRC, Boca Raton, Fl. 1994.
14. D.B. Denney and N. Sherman. J. Org. Chem. **30**, 3760 (1965).
15. (*a*) L.A. Paquette, W.H. Ham, and D.S. Dime. Tetrahedron Lett. **26**, 4983 (1985); (*b*) R.C. Gadwood, R.M. Lett, and J.E. Wissinger. J. Am. Chem. Soc. **108**, 6343 (1986); (*c*) K.S. Feldman, M.J. Wu, and D.P. Rotella. J. Am. Chem. Soc. **111**, 6457 (1989); (*d*) K.S. Feldman, M.J. Wu, and D.P. Rotella. J. Am. Chem. Soc. **112**, 8490 (1990); (*e*) G.A. Molander and P.R. Eastwood. J. Org. Chem. **60**, 4559 (1995); (*f*) A. Fürstner and K. Langemann. J. Org. Chem. **61**, 8746 (1996).
16. C.J. Cramer, M. Harmata, and P. Rashatasakhon. J. Org. Chem. **66**, 5641 (2001).
17. R.J. Giguere, S.M. Tassely, and M.I. Rose. Tetrahedron Lett. **31**, 4577 (1990).
18. J.H. Rigby and F.C. Pigge. Org. React. **51**, 351 (1997).
19. B. Simonot and G. Rousseau. J. Org. Chem. **59**, 5912 (1994).