JOC Article

A Tandem Metal Carbene Cyclization−Cycloaddition Approach to the Pseudolaric Acids

Bin Chen, Rebecca Y. Y. Ko, Mabel S. M. Yuen, Kin-Fai Cheng, and Pauline Chiu*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, PR China

pchiu@hku.hk

Received September 4, 2002

An approach toward the synthesis of the antifungal and cytotoxic pseudolaric acids based on the tandem metal carbene cyclization−cycloaddition reaction is described. Using this strategy, the advanced intermediate **3a** bearing three of the four stereocenters of the target molecules has been synthesized. The substrate-controlled diastereoselectivity of the tandem carbene cyclization−cycloaddition was preferential for the undesired diastereomer, but reagent control through the use of Hashimoto's chiral rhodium catalyst Rh_2(*S*-BPTV)$_4$ reversed the selectivity in favor of **3a**. Ring opening of the oxabicyclic nucleus to give a hydroxycycloheptene has been demonstrated in a model study.

Introduction

The root bark of *Pseudolarix kaempferi* Gordon (Pinaceae), a tree native to the Zhejiang province in China, has been harvested as a traditional Chinese medicine called *tujinpi* for the topological treatment of dermatological fungal infections as early as the 17th century.[1] From this preparation, a family of diterpenoids called the pseudolaric acids have been isolated. Pseudolaric acid B (**1b**) has been determined to be the main antifungal principle and has been evaluated to have activity comparable to that of amphotericin B against a number of strains of fungi.[2] In vitro tests of pseudolaric acids A, B, and C (**1a**−**c**) revealed their cytotoxicities to several cancer cell lines at submicromolar levels with low toxicity in vivo,[1b,3] with pseudolaric acids A and B being the more potent constituents.

Pseudolaric acids A, B, and C all possess the same characteristic perhydroazulene constitution with trans-fused acetoxy or hydroxy and lactone groups at the junctions, which is a rare arrangement for naturally occurring hydroazulenes.[4] Embedded in the common structure are a tertiary and three quaternary stereocenters lodged in a contiguous array. The overall compactness of the molecule also adds to the synthetic challenge posed by these natural products. Owing to their intriguing molecular architecture and promising biological activities, the pseudolaric acids have been the targets of a number of synthetic efforts.[5−9]

Our aim was to develop a convergent strategy to all of the members of the pseudolaric acid family. Previous approaches to these molecules based on an aldol cyclization as the key ring-forming reaction suffered from being unable to obtain the trans-fused 5,7-membered ring system as the major product.[5,8] Thus, alternative approaches that ensured the formation of this trans-ring junction were examined. To this end, we retroanalyzed these target molecules through a cleavage of the lactone functionality, a disconnection of a vinyl nucleophile at C11, back to a common enol triflate precursor 2 (Scheme 1). From this intermediate, pseudolaric acid A bearing a methyl substituent will be accessible via methylcuprate addition,[10] while pseudolaric acids B and C with carbomethoxy groups at C7 can be synthesized via palladium-catalyzed carbonylation.[11] This strategy permits flexibility for variations at C7,[12] and the methyl ketone at C3 allows for the addition of different groups at C11 for the synthesis of pseudolaric acid analogues.

Enol triflate **2** can in turn be obtained via a reductive elimination of oxatricyclic ketone **3**, in which the acetate of the tertiary alcohol at C4 has been masked as an

* Corresponding author. Tel: (852) 2859-8949. Fax: (852) 2857-1586.

(1) (a) Zhou, B. N.; Ying, B. P.; Song, G. Q.; Chen, Z. X.; Han, J.; Yan, Y. F. *Planta Med*. **1983**, *47*, 35. (b) Hamburger, M. O.; Shieh, H. L.; Zhou, B. N.; Pezzuto, J. M.; Cordell, G. A. *Magn. Res. Chem*. **1989**, *27*, 1025.

(2) Li, E.; Clark, A. M.; Hufford, C. D. *J. Nat. Prod*. **1995**, *58*, 57.

(3) Pan, D. J.; Li. Z. L.; Hu, C. Q.; Chen, K.; Chang, J. J.; Lee, K. H. *Planta Med*. **1990**, *56*, 383.

(4) Beyer, J.; Becker, H.; Toyota, M.; Asakawa, Y. *Phytochemistry* **1987**, *26*, 1085.

(5) Pan, B. C.; Chang, H. Y.; Cai, G. L.; Guo, Y. S. *Pure Appl. Chem*. **1989**, *61*, 389.

(6) Higuchi, R. I. Ph.D. Dissertation, Stanford University, Stanford, CA, 1995.

(7) (a) Bonk, J. D. Ph.D. Dissertation, University of Mississippi, MS, 1997. (b) Wu, B.; Karle, J. M.; Watkins, E. B.; Avery, M. A. *Tetrahedron Lett*. **2002**, *43*, 4095.

(8) (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett*. **1998**, *39*, 9229. (b) Chiu, P.; Chen, B.; Cheng, K. F. *Org. Lett*. **2001**, *3*, 1721.

(9) (a) Hu, Y.; Ou L.; Bai, D. *Tetrahedron Lett*. **1999**, *40*, 545. (b) Ou, L.; Hu, Y.; Song, G.; Bai, D. *Tetrahedron* **1999**, *55*, 13999.

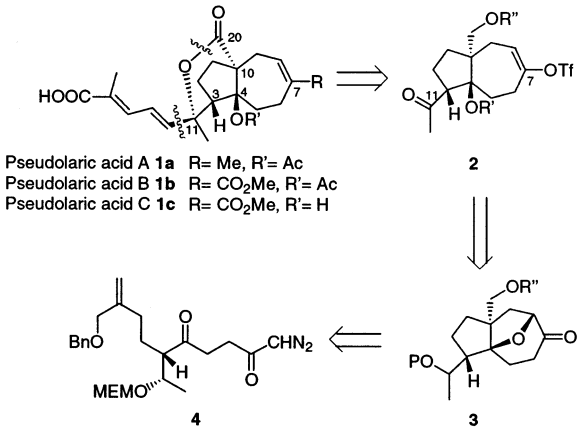
(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett*. **1980**, *21*, 4313.

(11) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1985**, *26*, 1109.

(12) Ritter, K. *Synthesis* **1993**, 735.

10.1021/jo026399m CCC: $25.00
Published on Web 04/25/2003

SCHEME 1. Retrosynthetic Analysis of Pseudolaric Acids A, B, and C



oxygen bridge. Oxatricyclic ketone **3** is envisioned as the key intermediate that could be constructed by a reaction cascade initiated by the decomposition of an appropriately functionalized acyclic diazo ketone **4**. This tandem carbene cyclization−intramolecular cycloaddition reaction[13] has been studied extensively by Padwa and coworkers.[14] This reaction was known to generate exclusively the cycloadduct with the oxygen bridge and the side chain at C10 in a trans relationship, as the alternative cis-fused adduct was extremely high in energy. Some applications of this powerful reaction for the synthesis of natural products have appeared.[15,16] Recently, a highly enantioselective tandem carbene cyclization intramolecular cycloaddition reaction using a chiral rhodium BINOL phosphate catalyst has been achieved.[17]

In this approach, the metal carbene derived from diazo ketone **4** would undergo intramolecular cyclization with the carbonyl group to form a six-membered cyclic carbonyl ylide, followed by a [3 + 2] cycloaddition with the 1,1-disubstituted olefin to give the oxatricyclic intermediate. Two aspects of this reaction in the context of the total synthesis have not been adequately explored in previous studies. According to our strategy, the carbonyl ylide is required to accomplish a dipolar cycloaddition with a tethered allylic ether, so that an alkoxy substituent at the bridgehead of the cycloadduct would be installed and could be further oxidized to ultimately generate the carboxylate at C20 of the pseudolaric acids. However, in the previous studies of this reaction, many of which were methodological in their aims, the olefins undergoing cycloaddition with the carbene-derived ylides were relatively simple; functionalized olefins, such as derivatives of allylic alcohols, have rarely been used as dipolarophiles.[18]

Furthermore, there were few reports dealing with the influence of preexisting stereocenters on the diastereoselectivity of the carbonyl ylide cycloaddition. Studies of this reaction cascade for the construction of the tigliane system by Dauben et al. showed that a number of stereocenters on the tether had no bearing on the stereochemistry of the carbonyl ylide cycloaddition.[15b] However, Maier's studies showed that cycloadditions of related isomünchnones generated from rhodium carbenes gave products with the α-substituent trans to the bridgehead substituent, a stereochemical result contrary to the requirements for the pseudolaric acids.[19]

Results and Discussion

Model Studies.

To address the first issue, a model substrate **12a** was prepared to ascertain the viability of an allylic ether as the dipolarophile in this tandem carbene cyclization−cycloaddition reaction (Scheme 2). Zinc homoenolate **5a** was alkylated with chloride **6a**[20] to give the homologated ester **7a** in 50% yield.[21] The use of bromide analogue **6b**, which was obtained efficiently from **6a**, escalated the yield of the allylation to 88%. Chain extension via a second homoenolate reaction with **5a** was initially planned, but neither the acid chloride nor the thioester derivative of **7a** gave good yields of coupled product under palladium catalysis.[22] However, conversion of ester **7a** to Weinreb amide **8a** allowed homologation via reaction with Normant's Grignard reagent **9**[23] to give hydroxy ketone **10a**. Oxidation to afford acid **11a**, followed by activation and treatment with diazomethane, produced the desired model diazo ketone substrate **12a**. Gratifyingly, the rhodium-catalyzed decomposition to the carbene and its subsequent cyclization−cycloaddition produced the expected trans cycloadduct **13** in 61% yield without incident.

Another model substrate **12b** with a substituent at C3 was prepared in an analogous manner. Starting from ester **7b**, an α-methyl group was appended by alkylation to give methylated substrate **7c** (Scheme 2). Following the analogous sequence of reactions employed for the preparation of **12a**, ester **7c** was homologated and

(13) Reviews: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Padwa, A. *Acc. Chem. Res.* **1991**, *I*, 22. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (d) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 3. (e) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic synthesis with Diazo Compounds*; J. Wiley & Sons: New York, 1998; Chapter 7, pp 397−416. (f) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.

(14) (a) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2875. (b) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817. (c) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Zhang, Z. J. *J. Org. Chem.* **1992**, *57*, 5747.

(15) Examples of carbene cyclization intramolecular cycloaddition: (a) McMills, M. C.; Zhuang L.; Wright, D. L. Watt, W. *Tetrahedron Lett.* **1994**, *35*, 8311. (b) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635.

(16) Examples of carbene cyclization intermolecular cycloaddition. Illudins and ptaquilosins: (a) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667. (b) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73. Zaragozic acids: (c) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185. (d) Hodgson, D. M.; Bailey, J. M.; Harrison, T. *Tetrahedron Lett.* **1996**, *37*, 4623. Brevicomin: (e) Padwa, A.; Fryxell, G. E. Zhi, L. *J. Am. Chem. Soc.* **1990**. *112*, 3100.

(17) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185.

(18) There is one example of a cycloaddition of an isomünchnone with a propargyl ether: Maier, M. E.; Schoffling, B. *Chem. Ber.* **1989**, *122*, 1081.

(19) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677.

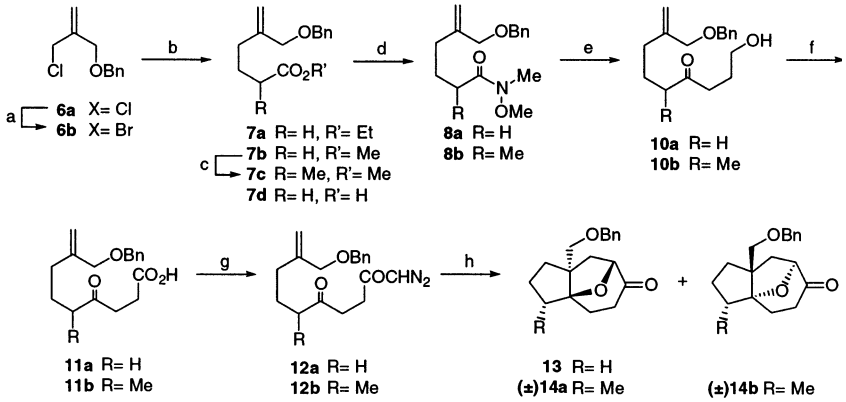
(20) van der Louw, J.; van der Baan, L. L.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 6087.

(21) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4420.

(22) (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth. Coll. Vol VIII*, 274. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559. (c) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

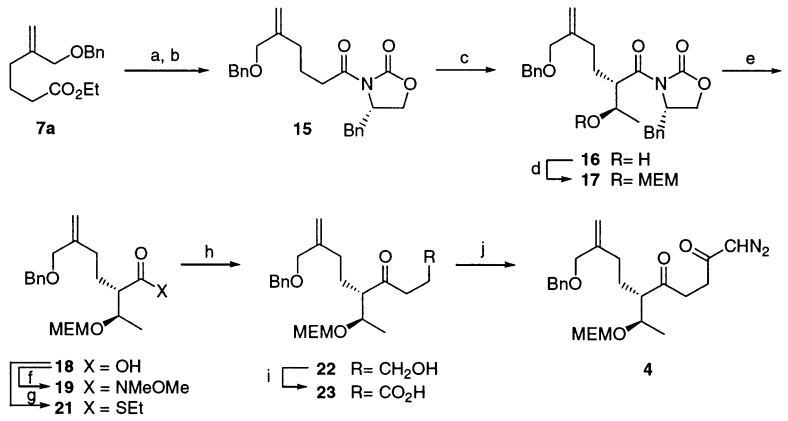
(23) Normant, J. F.; Cahiez, G.; Alexakis, A. *Tetrahedron Lett.* **1978**, *33*, 3013.

SCHEME 2. Synthesis of Model Diazo Precursors 12a and 12b[a]



[a] Reagents and Conditions: (a) LiBr, Aliquat 336, 60 °C, 97%; (b) $IZnCH_2CH_2CO_2Et$ **5a**, CuCN, THF, DMA, rt, 88% for **7a**, $IZnCH_2CH_2CO_2Me$ **5b,** 86% for **7b**; (c) (i) LDA, THF, −78 °C, (ii) MeI, 88%; (d) MeONHMe·HCl, Me_3Al, CH_2Cl_2, 92% for **8a**, 75% for **8b**; (e) $ClMg(CH_2)_3OMgCl$ **9**, CuI, THF, 92% for **10a**, 94% for **10b**; (f) PDC, DMF, H_2O, 71% for **11a**, 45% for **11b**; (g) (i) *i*-BuOCOCl, Et_3N, THF, −10 °C, (ii) CH_2N_2, Et_2O, 0 °C, 74% for **12a**, 68% for **12b**; (h) cat. $Rh_2(OAc)_4$, 61% for **13**, 63% total yield of **(±)-14a**:**(±)-14b**, 4:1.

SCHEME 3. Synthesis of Diazo Precursor 4[a]



[a] Reagents and Conditions: (a) NaOH, MeOH, 98%; (b) *t*-BuCOCl, Et_3N, DMAP, (*S*)-4-benzyl-2-oxazolidone, THF, −78 °C to room temperature, 80%; (c) (i) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; (ii) CH_3CHO, −78 to 0 °C, 67%, (92% based on recovered substrate); (d) MEMCl, DIPEA, CH_2Cl_2, rt, 93%; (e) (i) LiOH, H_2O_2, THF−H_2O, 0 °C, (ii) Na_2SO_3, 86%; (f) MeONHMe·HCl, *i*-Pr_2NEt, DCC, CH_2Cl_2, 44%; (g) EtSH, DCC, DMAP, CH_2Cl_2, rt, 91%; (h) $ClMg(CH_2)_3OMgCl$ **9**, CuI, THF, 77%, (93% based on recovered substrate); (i) PDC, DMF, H_2O, 75%; (j) (i) *i*-BuOCOCl, Et_3N, THF, −20 °C, (ii) CH_2N_2, Et_2O, 0 °C to room temperature, 72%.

elaborated in a straightforward manner to produce diazo ketone precursor **12b**. The tandem carbene cyclization−cycloaddition initiated by a catalytic amount of rhodium acetate produced two cycloadducts in 63% yield and in a ratio of 4:1 (Scheme 2). Gratifyingly, the major diastereomer was found to be **14a**, in which the methyl substituent and the benzyloxymethylene group were syn, as required in the structure of pseudolaric acid. The relative stereochemistry in **14a** was determined by the observation of an NOE between the methyl and the benzyloxymethylene protons, which showed that these groups were on the same side of the cyclopentane ring, and confirmed by the absence of this effect in isomer **14b**.

Preparation of the Chiral Precursor 4.

With these preliminary results in hand, the synthesis of the optically pure diazo ketone precursor **4** was undertaken (Scheme 3). The absolute stereochemistry at C3 was conferred using Evan's chiral auxiliary methodology.[24] Thus, ester **7a** was hydrolyzed to give acid **7d**, which was activated to synthesize the acylated oxazolidinone **15**. Aldol reaction via the boron enolate of **15** with acetaldehyde produced alcohol **16** as one diastereomer, which was subsequently protected as the MEM ether **17**.

Following the route previously worked out for model compound **12a**, transamination to give Weinreb amide **19** was the next step. Although the conversion of acyloxazolidinones directly to Weinreb amides is a well-documented methodology,[25] this transformation failed for the hindered substrate **17**. A variety of alkylaluminum amides reagents based on Me_3Al, Me_2AlCl, and Et_2AlCl were tried, but the major product isolated was urea **20**, resulting from the attack of the oxazolidone, accompanied by MEM ether cleavage (Scheme 4). Employing the unprotected alcohol **16** as substrate also resulted in the same product in 32% yield.

(24) (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.

(25) (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (b) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799. (c) Cane, D. E.; Tan, W.; Ott, W. R. . *J. Am. Chem. Soc.* **1993**, *115*, 527.

SCHEME 4. Transamination of Acyloxazolidones 16 and 17

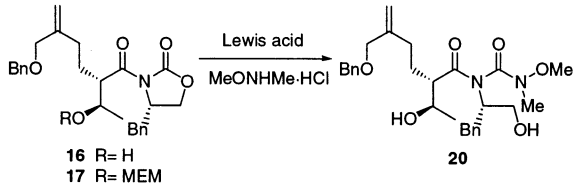
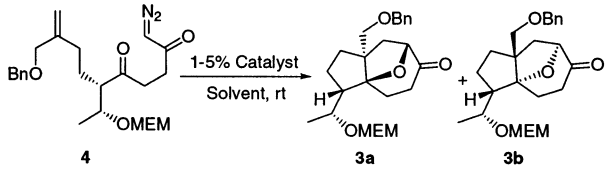


TABLE 1. Metal Carbene Cyclization−Cycloaddition of Diazo Ketone 4



entry	catalyst	solvent	product % yield	3a:3b
1	$Rh_2(OAc)_4$	CH_2Cl_2	61	**1:1.3**
2	$Rh_2(OAc)_4$	PhH	66	**1:1.2**
3	$Rh_2(OAc)_4$	CF_3Ph	45	**1:1.2**
4	$Rh_2(CAP)_4$	CH_2Cl_2	25	**1:1.2**
5	$Rh_2(OCOCF_3)_4$	CH_2Cl_2	61	**1:1.9**
6	$Rh_2(OCOCF_3)_4$	CF_3Ph	32	**1:1.2**

A two-step protocol was then attempted for the synthesis of Weinreb amide **19**. Hydrolysis of the acyloxazolidone **17** using lithium hydroperoxide produced acid **18**, which was activated by DCC for amidation. However, the conversion was extremely inefficient; reaction over 3 days produced amide **19** in only 44% yield. Similarly, coupling with BOP also resulted in a low yield of amide **19** (Scheme 3).

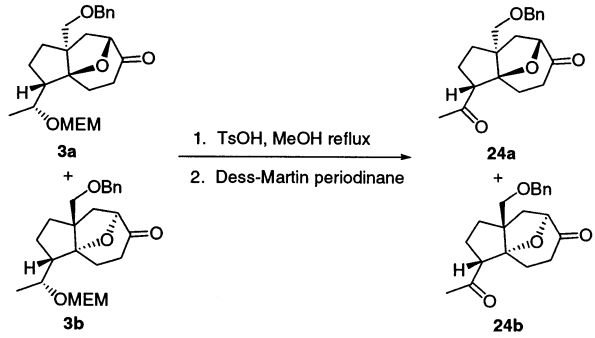
After some experimentation, a thioester was found to be a viable alternative electrophilic substrate for chain extension. Thus acid **18** was converted in high yield to thioester **21**, which was then homologated by the addition of the cuprate derived from Normant's Grignard reagent **9** to produce alcohol **22** in good yield.[26] Oxidation of the alcohol to acid **23**, followed by activation and treatment with diazomethane, generated the requisite chiral diazo ketone **4**.

Tandem Carbene Cyclization−Cycloaddition of 4. Diazo ketone **4** was subjected to treatment with a variety of rhodium catalysts. The results are summarized in Table 1. Diazo decomposition with a catalytic amount of dirhodium acetate produced, in one step, the oxatricyclic adduct **3** in 61% yield as two diastereomers **3a** and **3b** in a ratio of 1:1.3 (entry 1).

Elucidation of the structures of isomers **3a** and **3b** was initially hampered because the key proton signals belonging to H3 were superimposed on other upfield peaks in the ^{1}H NMR spectrum. Thus the cycloadducts **3a** and **3b** were converted to their ketone derivatives **24a** and **24b**, respectively, whose H3 were expected to absorb at more downfield chemical shifts. Compounds **3a** and **3b** obtained from the tandem cyclization−cycloaddition reaction were treated with acidic methanol to remove the MEM group, then the secondary alcohols were oxidized

(26) Anderson, R. J.; Henrick, C. A.; Rosenblum L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654.

SCHEME 5. Derivatization of 3a and 3b to Diketones 24a and 24b



with the Dess−Martin periodinane to afford ketones **24a** and **24b** (Scheme 5). The signal of H3 in ketone **24b** now appeared at δ 2.60 ppm, and its 2D-NOESY spectrum clearly showed an NOE between H3 and the benzyloxymethylene protons (δ 4.48 ppm). The structure of the minor compound **3a** was similarly determined by the analysis of its derivative **24a**, whose 2-D NOESY spectrum showed the absence of a cross-peak between H3 (δ 3.30 ppm) and the benzyloxymethylene protons at δ 4.49 ppm, confirming that the benzyloxymethylene substituent was in a cis relationship with the methyl ketone. Therefore, the major isomer possessed the structure as shown for **3b**, while the minor isomer **3a** was the desired diastereomer with the correct absolute stereochemistry for elaboration into the pseudolaric acids.

Other commercially available rhodium compounds were also tried as catalysts. Reaction of diazo ketone **4** with the less active dirhodium caprolactam was capricious but generally led to inferior yields of products (Table 1, entry 4). The more reactive dirhodium trifluoroacetate catalyst gave good yields of products, but the preference was even greater for the undesired isomer (Table 1, entry 5).

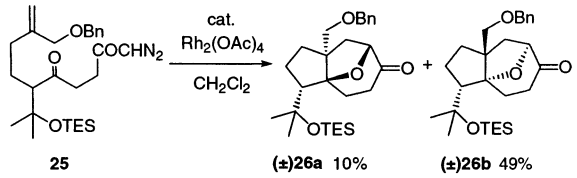
A solvent effect on the yield and the ratio of cycloadducts was observed. The decomposition of the diazo ketone and the subsequent tandem cyclization cycloaddition reaction proceeded rapidly in dichloromethane. Benzene was also an acceptable solvent, although with a more reactive catalyst such as dirhodium trifluoroacetate, the addition of the carbene to the aromatic ring was a major side reaction.[27] The use of benzotrifluoride[28] as a solvent generally gave similar yields of the cycloadducts compared to dichloromethane, but the formation of the desired isomer **3a** was more favored. Thus in the case of dirhodium trifluoroacetate, the reaction in benzotrifluoride improved to 1:1.2 from a ratio of 1:1.9 in dichloromethane (entry 6). However, in all these cases, the desired compound **3a** remained as the minor diastereomer.

Although our preliminary results in the tandem cyclization−cycloaddition of substrate **12b** gave the desired diastereomer **14a** with the C3 substituent being cis with respect to the bridgehead substituent, it is not clear why the analogous reaction of substrate **4** generated the

(27) Padwa, A.; Austin, D. J.; Hornbuckle, S. F. *J. Org. Chem.* **1996**, *61*, 63.

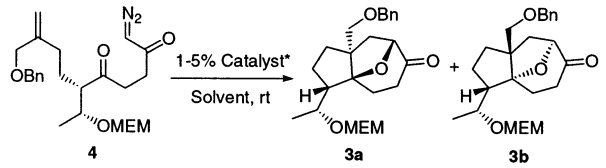
(28) (a) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (b) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

SCHEME 6. Tandem Cyclization−Cycloaddition of Diazo Ketone 25



25 (±)26a 10% (±)26b 49%

TABLE 2. Carbene Cyclization−Cycloaddition of Diazo Ketone 4 Using Chiral Catalysts



4 3a 3b

entry	catalyst	solvent	product % yield	**3a**:**3b**
1	Rh_2(*R*-MEPY)$_4$	CH_2Cl_2	17	**1**:**1.5**
2	Rh_2(*S*-MEPY)$_4$	CH_2Cl_2	13	**1**:**1.3**
3	Rh_2(*S*-MEOX)$_4$	CH_2Cl_2	0	
4	Rh_2(*R*-DOSP)$_4$	CH_2Cl_2	53	**1**:**1.3**
5	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	62	**1**:**1.7**
6	Rh_2(*S*-DOSP)$_4$	CF_3Ph	35	**1**:**1.3**
7	Rh_2(*S*-DDBNP)$_4$	CH_2Cl_2	54	**1**:**1.6**
8	Rh_2(*S*-BPTV)$_4$	CH_2Cl_2	67	**1.3**:**1**
9	Rh_2(*S*-BPTV)$_4$	CF_3Ph	51	**1.4**:**1**

opposite diastereomer as the major product. In fact, the increase in the steric demand of the C3 substituent in compound **4** over **12b** was initially expected to further enhance the factors that led to the predominance of **14a** over **14b**. It was surmised that perhaps the MEM ether at C11 was providing a chelating element that was not present in substrate **12b** and this resulted in an electron-donating perturbation of the original transition state. If this were the case, the use of a different protective group should restore the previously observed stereoselectivity. To see whether the MEM group was responsible for the reversal in the diastereoselectivity, a structurally similar diazo ketone **25**, whose hydroxyl group was protected as a noncoordinating triethylsilyl ether, was synthesized and subjected to treatment with catalytic rhodium (Scheme 6). The results of the tandem reaction was almost 5:1 in favor of the undesired diastereomer **(±)-26b**. Thus it appears that the change in the diastereoselectivity from the case of model compound **12b** was mainly due to an increase in the steric demands of the substituent at C3 in substrate **4**, which led to an undesirable steric interaction that was alleviated by cycloaddition in the opposite sense.

Tandem Carbene Cyclization−Cycloaddition of 4 Using Chiral Catalysts.

The recent results in highly enantioselective tandem carbene cyclization−cycloaddition reactions strongly suggest that the rhodium complex remains associated with the carbonyl ylide during the cycloaddition.[17,28a] Therefore, chiral rhodium catalysts were examined to see if reagent control could be exerted to overcome the substrate bias and direct the formation of the desired isomer **3a**. These results are summarized in Table 2. Commercially available chiral rhodium catalysts were investigated first. Catalysts based on chiral carboxamides[29] (entries 1−3) resulted in poor yields of the cycloadducts. The catalysts based on *N*-arylsulfonylprolinate ligands Rh_2(DOSP)$_4$ led to good yields of the cycloadducts,[30] but the stereochemical results of both the (*R*)- and (*S*)-enantiomeric catalysts remained in favor of the undesired diastereomer **3b** (entries 4−6). Although Hodgson's catalyst Rh_2(*R*-DDBNP)$_4$ was extremely successful in the enantioselective intramolecular cyclization−cycloaddition of a stabilized carbene, the diastereoselectivity of the reaction with our substrate was low (entry 7).[17] Finally, Hashimoto's catalyst Rh_2(*S*-BPTV)$_4$, which induced highly enantioselective carbene cyclization in tandem with intermolecular cycloadditions, was tried.[28a] To our relief, the ratio of cycloadducts was reversed in favor the desired isomer **3a** for the first time (entry 8). Switching the solvent from dichloromethane to benzotrifluoride further improved the ratio in favor of **3a** to 1.4:1 (entry 9).

Ring-Opening Studies Using Model Substrate 27.

While further optimization of the diastereoselectivity of the cyclization−cycloaddition of diazo ketone **4** was being pursued, reductive ring-opening strategies that would cleave the oxygen bridge of oxatricyclic compound **3a** toward intermediate **2** were also explored. This transformation was studied in the context of a simpler and more readily accessible oxatricyclic model compound **27**,[14b] which contains the essential elements of the oxatricyclic framework found in compound **3**.

Ring-opening at the oxygen bridge of oxabicyclo[2.2.1] ketones using single-electron reductants such as lithium or samarium iodide generated hydroxy ketones as products, and this transformation of oxapolycyclic substrates has been exploited in several syntheses.[16a,31] However, under the same reaction conditions, the reductive opening of oxabicyclo[3.2.1] systems with the carbonyl group in the two-carbon bridge was inefficient and apparently plagued by side reactions.[32] The facility of the ring opening in the [2.2.1] oxabicyclic series may be attributed in part to the greater strain in these systems.

In our synthesis, the carbonyl group of the oxatricyclic compound **3a** is situated in the three-carbon bridge. This should render flexibility to the ketyl anion to adopt an antiperiplanar position, leading to ring opening. Indeed, when model compound **27** was treated with samarium iodide, reduction with concomitant ring opening of the oxygen bridge occurred to give hydroxy ketone **29** as a 1:6 mixture with its hemiacetal form in 69% yield (Scheme 7). Alcohol **30**, obtained in single diastereomeric form as a minor product from the reduction, could in theory be reoxidized to ketone **27** and resubjected to reduction to improve the overall yield of the ring-opening reaction.

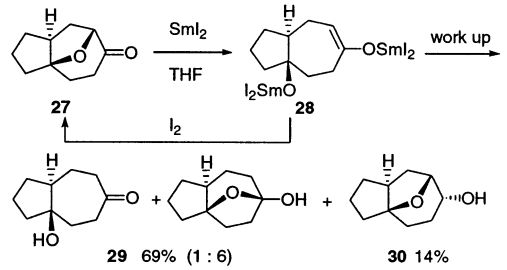
(29) (a) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (b) Doyle, M. P.; Dyatkin, A. B.; Protopopova, M. N.; Yang, C. I. Miertschin, C. S.; Winchester, W. R.; Simonsen, S. H.; Lynch, V.; Ghosh, R. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 163.

(30) (a) Davies, H. M. L. *Current Org. Chem.* **1998**, *2*, 463. (b) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107.

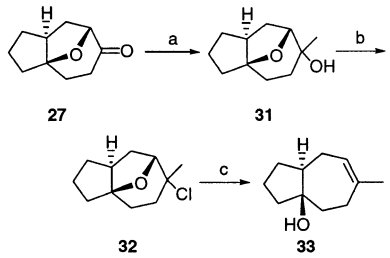
(31) (a) De Schrijver, J.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4369. Alternative photoreductive methods: (b) Cossy, J.; Ranaivosata, J. L.; Bellosta, V.; Ancerewicz, J.; Ferritto, R.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 0, 8351.(c) Cossy, J.; Aclinou, P.; Bellosta, V.; Furet, N.; Baranne-Lafont, J.; Sparfel, D.; Souchaud, C. *Tetrahedron Lett.* **1991**, *32*, 1315.

(32) Lautens, M.; Ma, S. *Tetrahedron Lett.* **1996**, *37*, 1727.

SCHEME 7. Ring-Opening Studies on Ketone 27



SCHEME 8. An Alternative Strategy for Oxygen-Bridge Cleavage[a]



[a] Reagents and Conditions: (a) MeMgI, Et_2O, 0 °C to room temperature, 2 h, 92%; (b) $SOCl_2$, DMAP, THF, 0 °C to room temperature; (c) Na, Et_2O reflux 5 h, 71% over two steps.

Since the reductive ring opening was successful in cleaving the oxygen bridge, efforts were then made to trap the intermediate enolate **28** formed en route to ketone **29** to retain the olefinic bond at C7 and C8. However, attempts to trap enolate **28** using a variety of reagents, including triflic anhydride, Comins' reagent,[33] TMSCl, or TMSOTf, were all unsuccessful. This might be attributed to the samarium−oxygen bond being very strong, and enolate **28** was thus resistant to transmetalation at the oxyanion. Although Motherwell et al. have reported the trapping of a samarium enolate, the product yields were consistently low.[34] Samarium enolate **28**, however, was reactive as an ambident nucleophile at carbon. When enolate **28** was treated with iodine, reaction rapidly occurred to regenerate the oxatricyclic substrate **27**, presumably via iodination of the enolate (Scheme 7). Ring opening using other reducing agents such as Zn and Zn/TMSCl were uniformly unsuccessful.

Thus an alternative strategy was used for the ring opening of ketone **27**, which also accomplished the synthesis of the trisubstituted double bond found in pseudolaric acid A (Scheme 8).[35] Treatment of substrate **27** with methyl Grignard reagent generated tertiary alcohol **31** as a single diastereomer.[36] The alcohol was converted to the volatile chloride **32**, which was reductively cleaved using sodium to yield ring-opened product **33** containing the requisite olefinic bond. Additional reductive ring-opening methodologies and strategies are being investigated.

(33) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1996**, *74*, 165.
(34) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211.
(35) Bromidge, S. M.; Sammes, P G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725.
(36) Although the stereochemistry of **31** was not rigorously established, it was presumed to be the α-alcohol on the basis of the characteristic reactivity patterns of oxabicyclic compounds; see: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

Conclusion

The synthesis of the key chiral intermediate **3a** containing three out of the four required stereocenters in the pseudolaric acids has been achieved in 12 steps from commercially available **6a** in an overall yield of 5.1%. The absolute stereochemistry at C3 was set by an asymmetric aldol reaction using Evan's chiral auxiliary. Chain elongation to obtain diazo ketone **4** was accomplished via thioester **21**. The optically pure tricyclic intermediate **3a** was obtained as the major diastereromer resulting from the tandem carbene cyclization−cycloaddition cascade reaction of diazo ketone **4**, using Hashimoto's chiral rhodium catalyst $Rh_2(S\text{-BPTV})_4$. Further investigations to improve the diastereoselectivity for **3a** are being conducted. Ring opening of the oxatricyclic core has been achieved in a model substrate **27** and these results will be applied to the actual intermediate. Elaborations of **3a** toward the completion of the total synthesis of the pseudolaric acids and their analogues are being actively pursued in our laboratory.

Experimental Section

General. All anhydrous reactions were performed in oven-dried glassware under a positive pressure of dry argon. Air- or moisture-sensitive reagents and anhydrous solvents were transferred with oven-dried syringes or cannulae using standard inert atmosphere techniques. All chemicals and solvents for reactions were used as received, unless otherwise mentioned. Tetrahydrofuran (THF) and diethyl ether were distilled from Na/Ph_2CO ketyl under argon. Dichloromethane, benzene, triethylamine, and diisopropylethylamine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide. Dimethylformamide (DMF) and *N*,*N*′-dimethylacetamide (DMA) were distilled from barium oxide under reduced pressure. Benzotrifluoride was refluxed and distilled from phosphorus pentoxide. Flash column chromatography was performed on E. Merck silica gel 60 (230−400 mesh ASTM) using EtOAc/*n*-hexane as eluents.

(2-Bromomethylallyloxymethyl)benzene (6b). To (2-chloromethylallyloxymethyl)benzene **6a**[20] (7.20 g, 36.64 mmol) and Aliquat 336 (0.70 g, 1.73 mmol) was added anhydrous LiBr (6.38 g, 73.47 mmol). The mixture was heated to 60 °C for 2 h. After cooling, the mixture was filtered on Florisil and washed with Et_2O. The volatiles were removed in vacuo to afford compound **6b** (8.53 g, 97% yield) as a pale yellow oil, which was used without further purification: R_f 0.75 (15% Et_2O/hexane); IR (film) 2935, 2858, 1612, 1513, 1468, 1252, 1174, 1093, 921, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.37 (s, 1H), 5.29 (s, 1H), 4.55 (s, 2H), 4.17 (s, 2H), 4.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 138.0, 128.5, 127.7 (2C), 117.3 72.4, 70.3, 33.1; LRMS (EI) *m*/*z* 161 (M^+ − Br, 23), 91 (100), 81 (56), 79 (61); HRMS (EI) *m*/*z* calcd for $C_{11}H_{13}O$ (M^+ − Br) 161.0966, found 161.0965.

5-Benzyloxymethyl-5-hexenoic Acid Ethyl Ester (7a). 3-Iodopropionic acid ethyl ester (ICH_2CH_2COOEt) was prepared from the corresponding bromide ($BrCH_2CH_2COOEt$) by a Finkelstein reaction.[37] 3-Iodopropionic acid ethyl ester (9.65 g, 43.86 mmol) and Zn(Cu)[38] (3.41 g, 52.46 mmol) in DMA (5.64 mL, 62.04 mmol) and THF (50 mL) were stirred at room temperature under argon for 2 h and then at 60 °C for 1 h to form homoenolate **5a**. This reaction mixture was filtered and transferred by cannula to bromide **6b** (8.24 g, 34.19 mmol) and CuCN (0.51 g, 5.70 mmol) in THF (30 mL). After stirring

(37) Sondheimer, F.; Rosenkranz, G.; Mancera, O.; Djerassi, C. *J. Am. Chem. Soc.* **1953**, *75*, 2601.
(38) Smith, R. D.; Simmons, H. E. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol. V, p 855.

overnight at room temperature, the mixture was quenched with saturated NH_4Cl. The organic phase was separated, washed sequentially with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue afforded compound **7a** (7.84 g, 88% yield) as a colorless oil: R_f 0.35 (15% Et_2O/hexane); IR (film) 2930, 2856, 1732, 1454, 1373, 1097, 1074, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.08 (s, 1H), 4.95 (s, 1H), 4.49 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.96 (s, 2H), 2.31 (t, J = 7.5 Hz, 2H), 2.13 (t, J = 7.7 Hz, 2H), 1.80 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 145.1, 138.3, 128.4, 127.7, 127.6, 112.4, 73.0, 72.0, 60.3, 33.9, 32.4, 22.8, 14.3; LRMS (EI) m/z 262 (M^+, 5), 231 (11), 171 (19), 156 (41), 91 (100); HRMS (EI) m/z calcd for $C_{16}H_{24}O_4$ 262.1569, found 262.1567.

5-Benzyloxymethyl-5-hexenoic Acid Methyl Ester (7b). Following the procedure for the preparation of compound **7a**, ester **7b** was prepared in a similar manner in 86% yield from ICH_2CH_2COOMe (69.5 g, 0.325 mol), Zn(Cu)[38] (24.56 g), DMA (38 mL, 0.464 mol), THF (320 mL), bromide **6b** (59.0 g, 0.245 mol), and CuCN (3.65 g, 0.041 mol). **7b**: a colorless oil; R_f (20% EtOAc in hexane) 0.67; IR (CH_2Cl_2) 3020, 2954, 2862, 1731, 1654, 1454, 1438, 1211, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.08 (s, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 3.96 (s, 2H), 3.66 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 2.13 (t, J = 7.7 Hz, 2H), 1.81 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 145.1, 138.4, 128.4, 127.7, 127.6, 112.4, 73.0, 72.0, 33.6, 32.5, 22.8; LRMS (EI) m/z 157 (M^+ − Bn, 18), 142 (40), 125 (15), 107 (16); HRMS (EI) m/z calcd for $C_8H_{13}O_3$ (M^+-Bn) 157.0865, found 157.0858.

Methyl 5-Benzyloxymethyl-2-methyl-5-hexenoate (7c). To a solution of ester **7b** (8.0 g, 32 mmol) in THF was added LDA (0.38 L, 0.1 M, 38.4 mmol) dropwise at −78 °C. After stirring for 30 min, MeI (6.0 mL, 96 mmol) was added. The reaction mixture was stirred for a further 30 min at −78 °C, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue afforded **7c** (7.4 g, 88%) as a pale yellow oil: R_f 0.63 (20% EtOAc/hexane); IR (film) 2953, 2862, 1729, 1454, 1365, 1168, 1072, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.22 (m, 5H), 5.06 (s, 1H), 4.93 (s, 1H), 4.49 (s, 2H), 3.94 (s, 2H), 3.63 (s, 3H), 2.63−2.39 (m, 1H), 2.10 (t, J = 7.7 Hz, 2H), 1.90−1.78 (m, 1H), 1.62−1.50 (m, 1H), 1.15 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.7, 145.1, 138.2, 128.1, 127.4, 127.3, 111.9, 72.8, 71.7, 51.2, 38.8, 31.4, 30.5, 16.8; LRMS (EI) m/z 262(17), 171 (18), 156 (30), 139 (21), 124 (8); HRMS (EI) m/z calcd for $C_{16}H_{24}O_4$ 262.1569, found 262.1572.

5-Benzyloxymethyl-5-hexenoic Acid *N,N′*-Methoxymethylamide (8a). To a suspension of MeONHMe·HCl (1.50 g, 15.10 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Me_3Al (7.60 mL, 15.20 mmol, 2 M in toluene) at 0 °C. After 1 h at room temperature, a solution of ester **7a** (1.31 g, 5.0 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C. After 12 h, the reaction was quenched by saturated NH_4Cl solution. The mixture was acidified by 0.5 N HCl to pH 4 and extracted with CH_2Cl_2 (4 × 15 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue afforded Weinreb amide **8a** (1.28 g, 92% yield) as a colorless oil: R_f 0.50 (40% EtOAc/hexane); IR (film) 2937, 2855, 1662, 1454, 1385, 1100, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.08 (s, 1H), 4.97 (s, 1H), 4.49 (s, 2H), 3.97 (s, 2H), 3.66 (s, 3H), 3.17 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H), 2.15 (t, J = 7.6 Hz, 2H), 1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (br), 145.4, 138.4, 128.4, 127.7, 127.5, 112.1, 73.0, 72.0, 61.2, 32.7, 32.2, 31.4, 22.4; LRMS (EI) m/z 277 (M^+, 2), 217 (4), 186 (9), 92 (7), 91 (100); HRMS (EI) $C_{16}H_{23}NO_3$ 277.1678, found 277.1680.

5-Benzyloxymethyl-2-methyl-5-hexenoic Acid *N,N′*-Methoxymethylamide (8b). Following the procedure for the preparation of compound **8a**, amide **8b** was prepared in a similar manner in 75% yield from ester **7c** (3.0 g, 11.5 mmol), MeONHMe·HCl (3.35 g, 34.4 mmol), and Me_3Al (17.2 mL, 34.4 mmol). **8b**: a colorless oil; R_f 0.16 (20% EtOAc/hexane); IR (film) 2939, 2898, 1648, 1457, 1389, 1074, 1029, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.25 (m, 5H), 5.06 (s, 1H), 4.95 (s, 1H), 4.48 (s, 2H), 3.95 (s, 2H), 3.64 (s, 3H), 3.16 (s, 3H), 2.88−2.87 (m, 1H), 2.11−1.93 (m, 2H), 1.91−1.82 (m, 1H), 1.59−1.49 (m, 1H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.4, 145.4, 138.2, 128.2, 127.9, 127.5, 127.3, 111.6, 72.8, 71.7, 61.2, 34.6, 31.2, 30.7, 29.5, 17.2; LRMS (EI) m/z 200 (M^+ − Bn, 11), 153 (11), 139 (11), 127 (13), 113 (16); HRMS (EI) m/z calcd for $C_{16}H_{24}O_4$ 200.1287, found 200.1287.

8-Benzyloxymethyl-1-hydroxy-8-nonen-4-one (10a). The Grignard reagent $ClMg(CH_2)_3OMgCl$ **9**[23] (10 mL, ∼0.5 M) was added to Weinreb amide **8a** (0.60 g, 2.17 mmol) in THF (5 mL) at 0 °C under argon. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue afforded compound **10a** (0.556 g, 92% yield) as a colorless oil: R_f 0.20 (40% EtOAc/hexane); IR (film) 3618, 2932, 2860, 1710, 1454, 1097, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.07 (s, 1H), 4.94 (s, 1H), 4.48 (s, 2H), 3.95 (s, 2H), 3.61 (t, J = 5.6 Hz, 2H), 2.53 (t, J = 6.9 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.09 (t, J = 7.4 Hz, 2H), 1.88−1.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 145.2, 138.3, 127.7, 127.6, 112.4, 72.9, 72.0, 42.2, 39.5, 32.4, 26.4, 21.5; LRMS (EI) m/z 276 (M^+, 3), 259 (7), 191 (17), 168 (28), 127 (100), 91 (36), 89 (23); HRMS (EI) m/z calcd for $C_{17}H_{21}O_3$ 273.1491, found 273.1489.

8-Benzyloxymethyl-1-hydroxy-5-methyl-8-nonen-4-one (10b). Following the procedure for the preparation of compound **10a**, alcohol **10b** was similarly prepared in 96% yield from ester **8b** (3.63 g, 1.25 mmol) and **9** (25 mL, ∼1.1M). **10b**: a colorless oil; R_f 0.26 (35% EtOAc/hexane); IR (film) 3610, 2938, 2884, 1708, 1454, 1370, 1102, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.23 (m, 5H), 5.05 (s, 1H), 4.92 (s, 1H), 4.46 (s, 2H), 3.93 (s, 2H), 3.65 (s, br, 1H), 3.53 (t, J = 6.2 Hz, 2H), 2.59−2.45 (m, 2H), 2.06−2.0 (m, 2H), 1.97−1.72 (m, 3H), 1.51−1.39 (m, 1H), 1.06 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 214.7, 145.0, 137.8, 128.0, 127.4, 127.2, 111.9, 72.5, 71.5, 61.3, 45.5, 40.4, 37.3, 30.3, 30.2, 26.3, 26.0, 16.2, 16.0, 11.3; LRMS (EI) m/z 272 (M^+ − H_2O, 5), 181 (10), 153 (13); HRMS (EI) m/z calcd for $C_{16}H_{24}O_4$ (M^+ − H_2O) 272.1776, found 272.1785.

8-Benzyloxymethyl-4-oxo-8-nonenoic Acid (11a). Alcohol **10a** (156 mg, 0.565 mmol) in 2.0 mL of DMF and 0.05 mL of H_2O was treated with PDC (1.28 g, 3.40 mmol) at room temperature for 8 h. Water (20 mL) was added and the mixture was extracted with EtOAc (5 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography of the residue afforded acid **11a** (110 mg, 71% yield) as a pale yellow oil. R_f 0.75 (75% EtOAc/hexane); IR (film) 3685, 3499, 2936, 1714, 1454, 1399, 1091, 1074, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.07 (s, 1H), 4.93 (s, 1H), 4.48 (s, 2H), 3.94 (s, 2H), 2.68 (m, 2H), 2,61 (m, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.08 (t, J = 7.3 Hz, 2H), 1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 178.3, 145.1, 138.2, 128.4, 127.7, 127.6, 112.5, 72.9, 72.0, 42.0, 36.8, 32.4, 27.7, 21.5; LRMS (EI) m/z 290 (M^+, 5), 245 (16), 199 (27), 154 (31), 91 (100); HRMS (EI) m/z calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1525.

8-Benzyloxymethyl-5-methyl-4-oxo-8-nonenoic Acid (11b). Following the procedure for the preparation of compound **11a**, acid **11b** was similarly prepared in 45% yield from alcohol **10b** (3.18 g, 10.9 mmol) and PDC (65.7 mmol, 24.7 g). **11b**: pale yellow oil; R_f 0.12 (20% EtOAc/hexane); IR (film) 3672, 3488, 2929, 1702, 1454, 1073, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.71 (s, br, 1H), 7.35−7.23 (m, 5H), 5.05 (s, 1H), 4.92 (s, 1H), 4.46 (s, 2H), 3.93 (s, 2H), 2.78−2.75 (m, 2H), 2.72−2.63 (m, 3H), 2.07−1.98 (m, 2H), 1.90−1.87 (m, 1H), 1.86−1.53 (m, 1H), 1.07 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,

75 MHz), δ 212.1, 178.0, 144.9, 137.9, 128.1, 127.4, 127.3, 112.1, 72.5, 71.5, 45.3, 35.1, 30.3, 27.4, 16.2; LRMS (EI) *m/z* 198 ($M^+ - Bn - CH_3$, 50), 180 (21), 167 (26), 153 (15), 139 (6); HRMS (ESI) *m/z* calcd for $C_{16}H_{24}O_4Na$ ($M^+ + Na$) 327.1572, found 327.1575.

9-Benzyloxymethyl-1-diazo-9-decene-2,5-dione (12a). To acid **11a** (121 mg, 0.417 mmol) in dry ether (2 mL) and THF (2 mL) at −20 °C was added Et_3N (0.097 mL, 0.698 mmol), followed by isobutyl chloroformate (0.090 mL, 0.694 mmol). The solution was stirred for 30 min and then warmed to 0 °C. Ethereal diazomethane[39] (3 mL, about 1.0 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and then reduced to one-third of its original volume. The residue was diluted with ether (10 mL); washed with water, saturated aqueous $NaHCO_3$, and brine; dried (Na_2SO_4); and concentrated in vacuo. Flash chromatography of the residue afforded diazo ketone **12a** (97 mg, 74% yield) as a yellow oil: R_f 0.40 (67% EtOAc/hexane); IR (film) 2930, 2896, 2108, 1734, 1717, 1645, 1385, 1099, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.30 (br s, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 4.48 (s, 2H), 3.95 (s, 2H), 2.75 (t, *J* = 6.2 Hz, 2H), 2.59 (br s, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.09 (t, *J* = 7.7 Hz, 2H), 1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 193.4, 145.2, 138.3, 128.4, 127.7, 127.6, 112.3, 72.9, 72.0, 54.5, 42.1, 39.6, 33.9, 32.4, 21.5.

9-Benzyloxymethyl-1-diazo-6-methyl-9-decene-2,5-dione (12b). Following the procedure for the preparation of substrate **12a**, diazo ketone **12b** was similarly prepared in 68% yield from acid **11b** (667 mg, 2.19 mmol), isobutyl chloroformate (0.284 mL, 2.19 mmol), and diazomethane (13 mL, about 4 mmol). **12b**: a yellow oil; R_f = 0.17 (20% EtOAc/hexane); IR (film) 2938, 2855, 2109, 1711, 1647, 1379, 1113, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.19 (m, 5H), 5.22 (br s, 1H), 4.99 (s, 1H), 4.87 (s, 1H), 4.41 (s, 2H), 3.88 (s, 2H), 2.82−2.67 (m, 2H), 2.56−2.45 (m, 3H), 2.02−1.95 (m, 2H), 1.85−1.74 (m, 1H), 1.48−1.33 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 193.5,145.3, 138.3, 128.3, 127.6, 127.5, 112.2, 72.9, 71.9, 53.4, 45.7, 385.3, 33.9, 30.6, 16.4; LRMS (EI) *m/z* 300 ($M^+ - N_2$, 27), 209 (91), 194 (23), 181 (23), 165 (22), 149 (30), 137 (20); HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_3$ ($M^+ - N_2$) 300.1725, found 300.1719.

(1*R,5*S**,7*R**)-5-Benzyloxymethyl-11-oxatricyclo-[5.3.1.0^{1,5}]undecan-8-one (13).** Diazo ketone **12a** (72 mg, 0.229 mmol) in dry benzene (5 mL) was treated with $Rh_2(OAc)_4$ (1 mg, 0.00226 mmol) and stirred for 6 h at room temperature. The reaction mixture was filtered and concentrated in vacuo. Chromatography of the residue afforded cycloadduct **13** (40 mg, 61% yield) as a colorless oil: R_f = 0.72 (33% EtOAc/hexane); IR (film) 2955, 2867, 1725, 1444, 1420, 1236 1085, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.49 (s, 2H), 4.31 (dd, *J* = 6.0, 3.5 Hz, 1H), 3.30 (q-AB, 2H), 2.53−1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 137.9, 128.4, 127.7, 127.6, 92.9, 82.2, 74.0, 73.5, 53.9, 42.4, 39.1, 37.5, 33.7, 26.1, 22.6; LRMS (EI) *m/z* 286 (M^+, 8), 195 (17), 150 (25), 137 (13), 123 (10), 119 (12), 95 (19), 91 (100), 79 (12); HRMS (EI) *m/z* calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1565.

(1*S,2*R**,5*S**,7*R**)-5-Benzyloxymethyl-2-methyl-11-oxatricyclo[5.3.1.0^{1,5}]undecan-8-one (14a) and (1*R**,2*R**,5*R**,7*S**)-5-Benzyloxymethyl-2-methyl-11-oxatricyclo[5.3.1.0^{1,5}]undecan-8-one (14b).** Diazo ketone **12b** (28.7 mg, 0.0874 mmol) in dry CH_2Cl_2 (1.0 mL) was treated with $Rh_2(OAc)_4$ (0.5 mg, 0.0011 mmol) for 2 h at 0 °C. The reaction mixture was filtered and concentrated in vacuo. Chromatography of the residue afforded cycloadduct **14a** (13.1 mg, 50% yield) as a colorless oil and cycloadduct **14b** (3.4 mg, 13% yield) as a colorless oil. **14a**: R_f = 0.48 (20% EtOAc/hexane); IR (film) 2956, 2919, 2871, 1721, 1462, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.27 (dd, *J* = 8.1, 0.5 Hz, 1H), 3.32 (d, *J* = 9.4 Hz, 1H), 3.29 (d, *J* = 9.4 Hz, 1H), 2.46 (ddd, *J* = 18.0, 11.3, 4.5 Hz, 1H), 2.36 (ddd, *J* = 18.1, 9.1, 4.5 Hz, 1H), 2.17 (m, 3H), 2.01 (dd, *J* = 12.9, 8.2 Hz, 1H), 1.89 (m, 2H), 1.59 (ddd, *J* = 13.1, 7.6, 2.4 Hz, 1H), 1.38 (m, 1H), 0.90 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 137.8, 128.4, 127.76, 127.74, 94.5, 82.1, 74.5, 73.6, 54.4, 43.5, 42.9, 36.7, 33.9, 30.3, 23.8, 14.3; LRMS (EI) *m/z* 300 (M^+, 33), 257 (10), 209 (18), 191 (24), 164 (66), 151 (83), 147 (100), 133 (42); HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_3$ (M^+) 300.1725, found 300.1726. **14b**: R_f 0.55 (20% EtOAc/hexane); IR (film) 2959, 2870, 1723, 1456, 1364, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.47 (s, 2H), 4.29 (d, *J* = 8.2 Hz, 1H), 3.30 (d, *J* = 9.4 Hz, 1H), 3.25 (d, *J* = 9.4 Hz, 1H), 2.48 (ddd, *J* = 18.0, 11.3, 4.6 Hz, 1H), 2.37 (ddd, *J* = 18.0, 9.2, 4.9 Hz, 1H), 2.19 (ddd, *J* = 13.8, 11.3, 4.9 Hz, 1H), 2.10 (dd, *J* = 13.0, 1.0 Hz, 1H), 1.99 (dd, *J* = 13.0, 8.3 Hz, 1H), 1.71 (m, 3H), 1.59 (m, 3H), 1.05 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 137.9, 128.4, 127.72, 127.65, 93.0, 82.0, 74.4, 73.5, 54.7, 43.2, 41.9, 36.8, 33.9, 30.7, 23.2, 12.6; LRMS (EI) *m/z* 300 (M^+, 34), 209 (20), 194 (15), 176 (19), 164 (71); HRMS (EI) *m/z* calcd for $C_{19}H_{24}O_3$ (M^+) 300.1725, found 300.1728.

(*S*)-Benzyl-3-(5-benzyloxymethyl-5-hexenoyl)oxazolidin-2-one (15). A solution of ester **7a** (7.80 g, 29.77 mmol) in MeOH (60 mL) was stirred vigorously with 10% NaOH (30 mL) at room temperature for 4 h. The methanol was removed in vacuo, and the residue was acidified with 10% HCl to pH 3 and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give acid **7d** (6.76 g, 97%) as colorless oil, which was pure and used without further purification. **7d:** R_f 0.15 (40% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.10 (s, 1H), 4.96 (s, 1H), 4.49 (s, 2H), 3.96 (s, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 144.8, 138.2, 128.4, 127.7, 127.6, 112.6, 72.9, 72.0, 33.4, 32.3, 22.5; IR (film, cm^{-1}) 3444 (br), 2940, 2867, 1709, 1454, 1274, 1096, 1072, 910; LRMS (EI) *m/z* 234 (M^+, 2), 143 (9), 128 (25), 125 (18), 107 (60), 91 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1259.

To acid **7d** (10.38 g, 44.36 mmol) and Et_3N (6.78 mL, 48.87 mmol) in THF (100 mL) was added pivaloyl chloride (6.08 mL, 48.87 mmol) slowly at −78 °C under argon. The thick white paste was allowed to stir at 0 °C for 1 h. A solution of (*S*)-4-benzyl-2-oxazolidinone[40] (7.80 g, 44.07 mmol), DMAP (0.70 g, 5.738 mmol), and Et_3N (6.12 mL) in THF (100 mL) was added to the mixed anhydride at −78 °C over 5 min. The mixture was stirred for 5 days at room temperature. The volatiles were removed in vacuo, and the resultant white paste was redissolved in CH_2Cl_2 (200 mL) and 1 M NaOH (100 mL). The aqueous phase was separated, the organic phase was washed with brine and dried (Na_2SO_4), and volatiles were removed in vacuo. The residue was purified by flash chromatography to give compound **15** (13.90 g, 80% yield) as a colorless oil. The basic aqueous phase was acidified and extracted to recover acid **7d** (1.40 g, 18% yield). **15:** R_f = 0.75 (50% EtOAc in hexane); IR (film) 2922, 2852, 1782, 1702, 1455, 1386, 1352, 1212, 1110, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10H), 5.10 (s, 1H), 4.99 (s, 1H), 4.66 (m, 1H), 4.50 (s, 2H), 4.16 (m, 2H), 3.99 (s, 2H), 3.29 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.96 (m, 2H), 2.75 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 153.5, 145.2, 138.4, 135.4, 129.5, 129.0, 128.4, 127.7, 127.6, 127.4, 112.4, 73.0, 72.0, 66.2, 55.2, 37.9, 35.1, 32.4, 22.1; LRMS (EI) *m/z* 393 (M^+, 2), 302 (33), 287 (94), 232 (64), 219 (29), 178 (77), 91 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1943; $[\alpha]^{20}_D$ = +20.6° (*c* 0.63, $CHCl_3$).

(1′*R*,2′*S*,4*S*)-4-Benzyl-3-[5-benzyloxymethyl-2′-(1′-hydroxyethyl)-5-hexenoyl]oxazolidin-2-one (16). To a solution of acylated oxazolidinone **15** (1.362 g, 3.466 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added dibutylboron

(39) (a) De Boer, Th. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV; p 250. (b) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.

(40) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.

triflate (4.16 mL, 4.16 mmol), followed by Et_3N (0.69 mL, 4.973 mmol) dropwise, keeping the internal temperature below 3 °C. The mixture was cooled to −78 °C and acetaldehyde (0.22 mL, 3.936 mmol) was added slowly. The solution was stirred at −78 °C for 20 min and then at 0 °C for 1 h. The reaction mixture was quenched by the addition of 12 mL of 2:1 methanol−30% aqueous hydrogen peroxide at such a rate as to keep the internal temperature below 10 °C. After the solution was stirred for 1 h, the volatiles were removed, and the resulting slurry was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography to give recovered substrate **15** (0.367 g, 27% yield) and aldol adduct **16** (1.018 g, 67% yield) as a pale yellow oil. **16:** R_f = 0.40 (50% EtOAc in hexane); IR (film) 3442, 2923, 2852, 1780, 1705, 1444, 1385, 1352, 1211, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10H), 5.07 (s, 1H), 4.98 (s, 1H), 4.70 (m, 1H), 4.47 (s, 2H), 4.12 (m, 4H), 3.98 (s, 2H), 3.35 (dd, J = 13.2, 3.1 Hz, 1H), 2.62 (dd, J = 13.2, 10.1 Hz, 1H), 2.52 (br s, 1H), 2.20−2.01 (m, 3H), 1.80 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 153.9, 145.2, 138.2, 135.3, 129.4, 129.0, 128.4, 127.7, 127.6, 127.4, 112.7, 72.9, 72.0, 68.9, 66.1, 55.7, 48.4, 38.0, 31.0, 25.5, 19.5; LRMS (EI) m/z 393 [M^+] (4), 302 [M − Bn]$^+$ (28), 287 (84), 232 (71), 219 (36), 178 (100); HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1939; $[\alpha]^{20}_D$ = +23.1° (c 0.36, $CHCl_3$).

(1′*R*,2′*S*,4*S*)-4-Benzyl-3-{5-benzyloxymethyl-2′-[1′-(2-methoxyethoxy)ethyl]-5-hexenoyl}oxazolidin-2-one (17). A solution of compound **16** (2.07 g, 4.74 mmol) in CH_2Cl_2 (10 mL) was treated with *i*-Pr_2NEt (1.75 mL, 10.07 mmol) and MEMCl (1.10 mL, 9.64 mmol) at room temperature. After stirring for 4 h, water (10 mL) was added and the resultant mixture was extracted with ether (3 × 30 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography to afford compound **17** (2.31 g, 93% yield) as a colorless oil. **17:** R_f = 0.48 (50% EtOAc in hexane); IR (film) 2928, 2887, 1779, 1701, 1454, 1385, 1198, 1108, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10H), 5.07 (s, 1H), 4.98 (s, 1H), 4.69 (s, 2H), 4.67 (m, 1H), 4.48 (s, 2H), 4.14 (m, 3H), 4.02 (t, J = 5.9 Hz 1H), 3.97 (s, 2H), 3.67 (m, 2H), 3.54 (m, 2H), 3.36 (s, 3H), 3.35 (dd, J = 13.2, 3.1 Hz, 1H), 2.64 (dd, J = 13.2, 10.2 Hz, 1H), 2.17−2.02 (m, 3H), 1.75 (m, 1H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 153.3, 145.3, 138.3, 135.5, 129.4, 128.9, 128.4, 127.7, 127.6, 127.4, 112.4, 93.9, 73.6, 72.9, 72.0, 71.8, 67.1, 65.9, 59.0, 55.9, 47.1, 37.9, 31.0, 25.9, 17.3; LRMS (EI) m/z 525 (M^+, 1), 450 (5), 358 (15), 330 (100), 304 (17), 178 (29), 91 (53), 89 (35); HRMS (EI) m/z calcd for $C_{30}H_{39}NO_7$ 525.2727, found 525.2726; $[\alpha]^{20}_D$ = +18.3° (c 0.81, $CHCl_3$).

(1′*R*,2*S*)-5-Benzyloxymethyl-2-[1′-(2-methoxyethoxymethoxy)ethyl]-5-hexenoic Acid (18). To a solution of oxazolidone **17** (2.0055 g, 3.82 mmol) in 25 mL of 4:1 THF−distilled water was added 0.91 mL of 50% aqueous H_2O_2 at 0 °C, followed by LiOH·H_2O (273.5 mg, 6.51 mmol) in distilled water (18 mL). After stirring for 3 h, sodium sulfite (1.204 g, 9.55 mmol) in 16 mL of distilled water was added. The bulk of the THF was removed in vacuo and the residue (pH 12−13) was extracted with CH_2Cl_2 (3 × 30 mL). The aqueous layer was cooled in an ice bath and acidified to pH 4. The resultant cloudy solution was extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford the desired acid **18** (1.1604 g, 83% yield) as a pale yellow oil. **18:** R_f = 0.21 (50% EtOAc in hexane); IR (film) 3475 (br), 2975, 2932, 2867,1712, 1455, 1383, 1107, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 5.08 (s, 1H), 4.97 (s, 1H), 4.78 (d, J = 7.2 Hz, 1H), 4.73 (d, J = 7.2 Hz, 1H), 4.49 (s, 2H), 3.98 (m, 1H), 3.96 (s, 2H), 3.70 (m, 2H), 3.54 (m, 2H), 3.38 (s, 3H), 2.58 (m, 1H), 2.15 (m, 2H), 1.82 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 145.0, 138.2, 128.4, 127.7, 127.6, 112.6, 94.1, 73.9, 72.9, 71.9 71.7, 67.1, 59.0, 50.8, 31.1, 25.9, 17.6; LRMS (EI) m/z 366 (M^+, 1), 291 (8), 247 (19), 232 (36), 170 (23), 141 (39), 91 (100), 89 (45); HRMS (EI) m/z calcd for $C_{20}H_{30}O_6$ 366.2042, found 366.2044; $[\alpha]^{20}_D$ = +29.8° (c 1.72, $CHCl_3$).

(1′*R*,2*S*)-5-Benzyloxymethyl-2-[1′-(2-methoxyethoxymethoxy)ethyl]-5-hexenoic Acid S-Ethyl Ester (21). To a solution of acid **18** (0.770 g, 2.104 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DMAP (0.016 g, 0.130 mmol), ethanethiol (0.31 mL, 4.145 mmol), and DCC (0.530 g, 2.573 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. Precipitated DCU was filtered off, and the filtrate was concentrated. The residue was taken up in CH_2Cl_2 and washed twice with 0.5 N HCl and then with saturated $NaHCO_3$ and brine. The solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography to afford thioester **21** (0.790 g, 91% yield) as a colorless oil. **21:** R_f= 0.82 (33% EtOAc in hexane); IR (film) 2973, 2930, 2882, 1682, 1454, 1458, 1248, 1078, 1036, 906, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.08 (s, 1H), 4.96 (s, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.71 (d, J = 7.2 Hz, 1H), 4.48 (s, 2H), 3.95 (s, 2H), 3.88 (m, 1H), 3.70 (m, 2H), 3.54 (m, 2H), 3.38 (s, 3H), 2.88 (q, J = 7.4 Hz, 2H), 2.70 (m, 1H), 2.10 (m, 2H), 1.86 (m, 2H), 1.82 (m, 3H), 1.24 (t, J = 7.4 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 145.2, 138.4, 128.3, 127.7, 127.5, 112.3, 94.2, 74.3, 73.0, 71.9, 71.7, 67.1, 59.7, 59.0, 30.7, 27.0, 23.4, 18.2, 14.7; LRMS (EI) m/z 321 (M^+ − MEM, 5), 273 (15), 215 (24), 153 (22), 91 (100), 89 (36); HRMS (EI) m/z calcd for $C_{22}H_{34}O_5S$ (M^+ − MEM) 321.1534, found 321.1528; $[\alpha]^{20}_D$ = +36.7° (c 1.32, $CHCl_3$).

(1′*R*,5*S*)-8-Benzyloxymethyl-1-hydroxy-5-[1′-(2-methoxyethoxymethoxy)ethyl]-8-nonen-4-one (22). Grignard reagent **9** (10 mL, 5 mmol) was added into thioester **21** (0.680 g, 1.659 mmol), Me_2S (1.20 mL), and CuI (1.43 g, 7.5 mmol) suspended in THF (10 mL) at 0 °C. The resultant mixture was stirred at room temperature overnight and quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography to give alcohol **22** (0.52 g, 77% yield), as a colorless oil, and unreacted thioester **21** (116 mg, 17%). **22:** R_f = 0.25 (67% EtOAc in hexane); IR (film) 3480 (br), 1708, 1454, 1375, 1245, 1097, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 5.06 (s, 1H), 4.93 (s, 1H), 4.76 (d, J = 7.1 Hz, 1H), 4.71 (d, J = 7.1 Hz, 1H), 4.47 (s, 2H), 3.93 (s, 2H), 3.90 (m, 1H), 3.69 (m, 2H), 3.56 (m, 4H), 3.39 (s, 3H), 2.78 (m, 2H), 2.52 (dt, J = 18.3, 6.6 Hz, 1H), 2.26 (br s, 1H), 2.00 (m, 2H), 1.82 (m, 3H), 1.62 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 145.3, 138.2, 128.4, 127.7, 127.6, 112.5, 93.9, 74.1, 72.9, 72.0, 71.7, 67.2, 61.9, 59.0, 56.7, 41.5, 31.1, 26.0, 25.9, 17.3; LRMS (EI) m/z 302 (M^+ − MEM − OH, 4), 375 (2), 301 (4), 284 (18), 257 (15), 195 (37), 193 (70), 174 (40), 91 (100), 89 (64); HRMS (EI) m/z calcd for $C_{19}H_{26}O_3$ (M^+ − MEM − OH) 302.1882, found 302.1880; $[\alpha]_D$ = +17.5° (c 0.76, $CHCl_3$).

(1′*R*,5*S*)-8-Benzyloxymethyl-5-[1′-(2-methoxyethoxymethoxy)ethyl]4-oxo-8-nonenoic Acid (23). Following the procedure for the preparation of acid **11a**, acid **23** was similarly prepared in 75% yield from alcohol **22** (88 mg, 0.216 mmol) and PDC (0.49 g, 1.293 mmol). **23:** a colorless oil; R_f = 0.18 (75% EtOAc in hexane); IR (film) 3502, 2930, 1712, 1456, 1384, 1112, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 7.37−7.25 (m, 5H), 5.06 (s, 1H), 4.93 (s, 1H), 4.76 (d, J = 7.1 Hz, 1H), 4.71 (d, J = 7.1 Hz, 1H), 4.47 (s, 2H), 3.93 (s, 2H), 3.88 (m, 1H), 3.68 (m, 2H), 3.54 (m, 2H), 3.38 (s, 3H), 2.88 (m, 1H), 2.72 (m, 2H), 2.57 (m, 2H), 2.02 (m, 2H), 1.90 (m, 1H), 1.62 (m, 1H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 177.9, 145.2, 138.2, 128.3, 127.7, 127.5, 112.4, 93.9, 74.0, 72.8, 71.9, 71.7, 67.1, 59.0, 56.4, 39.3, 31.0, 27.5, 25.9, 17.1; LRMS (EI) m/z 333 (M^+ − MEM, 6), 391 (5), 347 (9), 242 (28), 197 (31), 91 (100); HRMS (EI) m/z calcd for $C_{19}H_{25}O_5$ (M^+ − MEM) 333.1702, found 333.1699; $[\alpha]^{20}_D$ = +24.1° (c 0.69, $CHCl_3$).

(1′*R*,6*S*)-9-Benzyloxymethyl-1-diazo-6-[1′-(2-methoxyethoxymethoxy)ethyl]-9-decene-2,5-dione (4). Following the procedure for the preparation of diazo ketone **12a**, diazo ketone **4** was prepared in a similar fashion in 72% yield from acid **23** (120 mg, 0.294 mmol), Et_3N (0.061 mL, 0.439 mmol), isobutyl chloroformate (0.057 mL, 0.440 mmol), and ethereal diazomethane (3 mL, about 1.0 mmol). **4:** a yellow oil; R_f = 0.23 (40% EtOAc in hexane); IR (film) 2929, 2896, 2108, 1711, 1644, 1380, 1100, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.28 (br s, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 4.76 (d, J = 7.1 Hz, 1H), 4.71 (d, J = 7.1 Hz, 1H), 4.48 (s, 2H), 3.94 (s, 2H), 3.88 (m, 1H), 3.68 (m, 2H), 3.54 (m, 2H), 3.38 (s, 3H), 2.95 (dt, J = 18.9, 6.4 Hz, 1H), 2.78 (m, 2H), 2.55 (br m, 2H), 2.01 (m, 2H), 1.86 (m, 1H), 1.60 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 193.4, 145.3, 138.4, 128.4, 127.7, 127.6, 112.4, 94.0, 74.1, 72.9, 72.0, 71.7, 67.2, 59.1, 56.5, 54.5 (br), 39.4 (br), 33.9 (br), 31.1, 26.1, 17.2; LRMS (EI) m/z 418 ($M^+ - N_2$, 18), 342 (66), 312 (22), 299 (30), 285 (32), 251 (28), 233 (17); HRMS (EI) m/z calcd for $C_{24}H_{34}O_6$ ($M^+ - N_2$) 418.2355, found 418.2361; $[\alpha]^{20}_D$ = +19.9° (c 5.85, $CHCl_3$).

(1*S*,1′*R*,2*S*,5*S*,7*R*)-5-Benzyloxymethyl-2-[1′-(2-methoxyethoxymethoxy)ethyl]-11-oxatricyclo[5.3.1.0^{1,5}]-8-undecanone (3a) and (1*R*,1′*R*,2*S*,5*R*,7*S*)-5-Benzyloxymethyl-2-[1′-(2-methoxyethoxymethoxy)ethyl]-11-oxatricyclo[5.3.1.0^{1,5}]-8-undecanone (3b). A solution of diazo ketone **4** (10.1 mg, 0.0226 mmol) in dry benzotrifluoride (1.0 mL) was treated with Rh_2(*S*-BPTV)$_4$ (0.3 mg, 2.26 × 10^{-4} mmol) at 0 °C for 2.5 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography to give product **3** (5.7 mg, 51% yield, **3a**:**3b** = 1.4:1).

HPLC separation of the mixture of **3a** and **3b** gave analytically pure samples of **3a** and **3b**. **3a:** a colorless oil; R_f = 0.48 (40% EtOAc in hexane); IR (CH_2Cl_2) 2935, 2874, 1728, 1456, 1362, 1103, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.60 (d, J = 7.0 Hz, 1H), 4.57 (d, J = 7.1 Hz, 1H), 4.50 (s, 2H), 4.32 (br d, J = 6.6 Hz, 1H), 3.87 (dq, J = 6.3, 2.2 Hz, 1H), 3.62 (m, 1H), 3.53 (q, J = 4.1 Hz, 1H), 3.50 (s, 2H), 3.48 (d, J = 9.2 Hz, 1H), 3.46 (d, J = 9.2 Hz, 1H), 3.38 (s, 3H), 2.61 (dt, J = 17.7, 8.9 Hz, 1H), 2.36 (m, 1H), 2.22 (m, 1H), 2.18 (m, 2H), 2.12 (m, 1H), 2.01 (m, 1H), 1.91 (m, 3H), 1.66 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 138.2, 128,4, 127.7, 127.7, 94.7, 94.2, 82.4, 73.5, 73.1, 71.8, 71.4, 67.5, 59.1, 56.2, 53.8, 40.6, 37.7, 33.1, 25.9, 24.3, 19.3; LRMS (EI) m/z 418 (M^+, 2), 342 (16), 329 (11) 299 (15), 221 (36),111 (49), 89 (100); HRMS (EI) m/z calcd for $C_{24}H_{34}O_6$ 418.2355, found 418.2360; $[\alpha]^{20}_D$ = −26.3° (c 0.11, $CHCl_3$). **3b:** a colorless oil; R_f = 0.43 (40% EtOAc in hexane); IR (CH_2Cl_2) 2934, 2874, 1728, 1455, 1364, 1103, 1037 cm^{-1};^1H NMR (600 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 4.76 (q-AB, 2H), 4.48 (s, 2H), 4.31 (t, J = 4.8 Hz, 1H), 4.05−4.04 (m, 1H), 3.78−3.75 (m, 1H), 3.73−3.69 (m, 1H), 3.54 (t, J = 4.7 Hz, 2H), 3.38 (s, 2H), 3.30 (q-AB, 2H), 2.47−2.35 (m, 3H), 2.01 (d, J = 4.8 Hz, 2H), 1.91−1.84 (m, 1H), 1.83−1.74 (m, 4H), 1.63−1.60 (m, 2H), 1.29 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.1, 137.8, 128.4, 127.8, 127.6, 94.2, 92.4, 82.4, 77.5, 74.2, 73.5, 72.1, 71.9, 67.0, 59.1, 56.2, 52.6, 42.1, 36.4, 33.7, 24.9, 24.7, 20.6; LRMS (EI) m/z 418 (M^+, 2), 342 (20), 329 (9) 299 (12), 221 (45), 111 (44), 89 (100); HRMS (EI) m/z calcd for $C_{24}H_{34}O_6$ 418.2355, found 418.2360; $[\alpha]^{20}_D$ = +16.3° (c 0.11, $CHCl_3$).

(1*S*,2*R*,5*S*,7*R*)-2-Acetyl-5-benzyloxymethyl-11-oxatricyclo[5.3.1.0^{1,5}]-8-undecanone (24a) and (1*R*,2*R*,5*R*,7*S*)-2-Acetyl-5-benzyloxymethyl-11-oxatricyclo[5.3.1.0^{1,5}]-8-undecanone (24b). A mixture of **3a** and **3b** (**3a**:**3b** = 1:1.25, 40 mg, 0.096 mmol) and TsOH (37 mg, 0.20 mmol) in MeOH (3 mL) was heated to reflux for 1 h. MeOH was removed in vacuo. The residue was taken up in 5 mL of EtOAc, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography to afford a mixture of alcohols (25 mg, 80%) as a colorless oil.

To the alcohols (25 mg, 0.076 mmol) in dry CH_2Cl_2 (1 mL) was added the Dess−Martin reagent[41] (50 mg, 0.12 mmol) at room temperature. After stirring for 6 h, saturated $Na_2S_2O_3$ solution was added dropwise until the reaction mixture cleared up. Saturated $NaHCO_3$ was added and the solution was extracted with EtOAc (3 × 5 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography to afford a mixture of **24a** and **24b** (**24a**:**24b** = 1.25:1, 23 mg, 93%) as a colorless oil.

Careful separation of the mixture of **24a** and **24b** by column chromatography gave pure samples of **24a** and **24b** for analytical purposes. **24a:** R_f = 0.65 (40% EtOAc in hexane); IR (CH_2Cl_2) 2958, 2938, 2869, 1726, 1709, 1455, 1364, 1104, 1088, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.52 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.30 (d, J = 7.4 Hz, 1H), 3.62 (d, J = 9.2 Hz, 1H), 3.44 (d, J = 9.2 Hz, 1H), 3.33 (dd, J = 8.3, 2.2 Hz, 1H), 2.38 (m, 3H), 2.25 (m, 1H), 2.21 (s, 3H), 2.15 (q, J = 6.9 Hz, 1H), 2.03 (dd, J = 8.8, 6.9 Hz, 1H), 1.98 (dd, J = 12.8, 8.3 Hz, 1H), 1.83 (ddd, J = 6.6, 3.7, 2.5 Hz, 1H), 1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 209.5, 137.9, 128.4, 127.8, 127.6, 93.3, 82.4, 73.4, 72.5, 61.5, 54.9, 42.0, 37.9, 33.8, 31.2, 27.2, 24.6; LRMS (EI) m/z 328 (M^+, 19), 237 (26), 194 (100), 179 (53), 149 (67); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1672; $[\alpha]^{20}_D$ = −22.9° (c 0.18, $CHCl_3$). **24b**: R_f = 0.65 (40% EtOAc in hexane); IR (CH_2Cl_2) 2960, 2929, 2865, 1726, 1695, 1455, 1358, 1104, 1076, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.48 (s, 2H), 4.37 (dd, J = 5.3, 4.2 Hz, 1H), 3.33 (d, J = 9.5 Hz, 1H), 3.27 (d, J = 9.5 Hz, 1H), 2.60 (dd, J = 11.8, 6.4 Hz, 1H), 2.47−2.29 (m, 4H), 2.25 (s, 3H), 2.042 (d, J = 5.5 Hz, 1H), 2.039 (d, J = 4.0 Hz, 1H), 1.90 (m, 3H), 1.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 209.2, 137.5, 128.5, 127.9, 127.6, 92.7, 82.7, 73.6, 73.5, 60.1, 55.3, 42.0, 36.6, 33.6, 30.3, 26.3, 23.9; LRMS (EI) m/z 328 (M^+, 23), 237 (33), 194 (100), 179 (45), 149 (60); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1670; $[\alpha]^{20}_D$ = +13.6° (c 0.13, $CHCl_3$).

(1*S,2*R**,5*S**,7*R**)-5-Benzyloxymethyl-2-(1-methyl-1-triethylsiloxyethyl)-11-oxatricyclo[5.3.1.0^{1,5}]undecan-8-one (26a) and (1*R**,2*R**,5*R**,7*S**)-5-Benzyloxymethyl-2-(1-methyl-1-triethylsiloxyethyl)-11-oxatricyclo[5.3.1.0^{1,5}]-undecan-8-one (26b).** A solution of diazo ketone **25** (20.7 mg, 0.0425 mmol) in dry CH_2Cl_2 (1 mL) was treated with $Rh_2(OAc)_4$ (0.18 mg, 4.25 × 10^{-4} mmol) for 3.5 h at 0 °C. Workup and chromatography afforded a mixture of cycloadducts **26a** and **26b** (11.5 mg, 59%, **26a**:**26b** = 1:4.9). **26a**: a colorless oil; R_f = 0.61 (20% EtOAc in hexane); IR (film) 2959, 2877, 1726, 1456, 1366, 1105, 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 4.52 (q-AB, 2H), 4.35 (br d, J = 8.4 Hz, 1H), 3.47 (d, J = 9.1 Hz, 1H), 3.39 (d, J = 9.2 Hz, 1H), 2.91−2.84 (m, 1H), 2.50−2.43 (m, 1H), 2.38−2.33 (m, 1H), 2.24 (dd, J = 7.8 Hz, 11.0 Hz, 1H), 2.17−2.12 (m, 1H), 2.05−1.96 (m, 2H), 1.93−1.88 (m, 1H), 1.73−1.65 (m, 1H), 1.61−1.55 (m, 1H), 1.34 (s, 3H), 1.18 (s, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 139.1, 128.5, 127.8, 127.7, 95.1, 83.4, 75.0, 73.6, 71.9, 60.5, 57.3, 40.4, 36.4, 33.3, 31.6, 29.9, 29.3, 26.2, 7.2, 6.9; LRMS (EI) m/z 427 ($M^+ - C_2H_5$, 93), 411 (12), 305 (44), 291 (15), 235 (40), 217 (36); HRMS (EI) m/z calcd for $C_{25}H_{37}O_4Si$ ($M^+ - C_2H_5$) 429.2461, found 429.2462. **26b**: a colorless oil; R_f = 0.68 (20% EtOAc in hexane); IR (film) 2957, 2876, 1724, 1456, 1365, 1130, 1103, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.50 (s, 2H), 4.29 (dd, J = 7.4, 2.3 Hz, 1H), 3.36 (d, J = 9.3 Hz, 1H), 3.30 (d, J = 9.3 Hz, 1H), 3.10−3.04 (m, 1H), 2.40−2.36 (m, 2H), 2.01−1.91 (m, 3H), 1.82−1.64 (m, 4H), 1.56−1.51 (m, 1H) 1.36 (s, 3H), 1.25 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 8.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

(41) Boeckman Jr., R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141.

212.1, 138.0, 128.4, 127.7, 127.6, 93.3, 82.3, 76.4, 74.3, 73.5, 57.3, 56.3, 42.1, 36.4, 33.7, 32.1, 27.3, 26.2, 25.7, 7.2, 6.9; LRMS (EI) *m*/*z* 429 (M^+- C_2H_5, 51), 265 (93), 218 (8), 205 (20), 191 (34), 173 (49); HRMS (EI) *m*/*z* calcd for $C_{25}H_{37}O_4Si$ ($M^+ - C_2H_5$) 429.2461, found 429.2460.

Reductive Cleavage of Compound 27. To a solution of ketone **27**[14] (110 mg, 0.663 mmol) in THF (2 mL) was added SmI_2 (0.1 M in THF, 14.6 mL, 1.460 mmol) at 0 °C under Ar. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with pH = 7 phosphate buffer (2 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography to give compounds **29** [76 mg, 69% yield, **29a** (keto form):**29b** (hemiacetal) = 0.14: 0.86] and **30** (16 mg, 14% yield), both as colorless oils. **29**: R_f 0.40 (33% EtOAc/hexane); IR (film) 3347 (br), 2959, 2877, 1721, 1454, 1236, 1090, 1040, 938 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 0.86 × 1H), 2.94 (dt, J = 14.1, 3.8 Hz, 0.14 × 1H), 2.50 (m, 0.14 × 2H), 2.32 (m, 0.14 × H) 2.16−1.48 (m, 0.86 × 15H + 0.14 × 12H); ^{13}C NMR (75 MHz, $CDCl_3$) **29a**: δ 214.8, 79.9, 50.6, 43.5, 41.7, 38.2, 34.8, 30.7, 21.9, 19.7. **29b**: δ 103.8, 90.5, 50.6, 34.9, 34.4, 32.6, 30.9, 27.9, 21.6, 21.2; LRMS (EI) *m*/*z* 168 (M^+, 11), 151 (100), 123 (35), 95 (29); HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1146. **30**: R_f = 0.25 (33% EtOAc/hexane); IR (film) 3400 (br), 2944, 2869, 1464, 1456, 1351, 1149, 1128, 1066, 1010, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (dd, J = 6.4, 4.5 Hz, 1H), 3.82 (m, 1H), 2.33−2.22 (m, 2H), 1.97−1.81 (m, 5H), 1.66−1.35 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.5, 80.4, 68.1, 45.7, 36.2, 34.8, 34.0, 32.8, 28.0, 26.0; LRMS (EI) *m*/*z* 168 (M^+, 16), 124 (100), 97 (43); HRMS (EI) *m*/*z* calcd for $C_{18}H_{22}O_3$ 168.1150, found 168.1153. The J_{ax-ax} = 6.4 Hz of the downfield signal at 4.26 ppm implies an axial proton, and thus, the hydroxyl group in **30** is α.

8-Methyl-11-oxatricyclo[5.3.1.0^{1,5}]undecan-8-ol (31). To a solution of ketone **27** (83 mg, 0.50 mmol) in Et_2O (2 mL) was added MeMgI at 0 °C under argon. The reaction mixture was stirred for 2 h at room temperature and then quenched using saturated NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organics were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography to give alcohol **31** (84 mg, 92% yield, one diastereoisomer) as a colorless oil: R_f 0.35 (33% EtOAc in hexane); IR (film, cm^{-1}) 3391 (br), 2943, 2869, 1694, 1454, 1334, 1265, 1167, 1093, 1039, 1009, 948; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, J = 7.1 Hz, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 1.91−1.40 (m, 12H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 93.0, 84.8, 69.7, 45.1, 36.2, 35.1, 34.7, 33.6, 32.4, 29.7, 26.3, 25.8; LRMS (EI) *m*/*z* 182 (M^+, 17), 139 (47), 138 (100), 111 (48), 95 (46); HRMS (EI) *m*/*z* calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1305.

(3a*R,8a*S**)-6-Methyl-2,3,4,5,8,8a-hexahydro-1H-azulen-3a-ol (33).** To a solution of alcohol **31** (90 mg, 0.495 mmol) in DMPU (0.54 mL) was added $SOCl_2$ (0.090 mL, 0.617 mmol) at 0 °C under Ar. The reaction mixture was stirred overnight then quenched with water (2 mL). The resulting mixture was extracted with ether (3 × 5 mL). The combined organics were washed with water, dried over $MgSO_4$, and removed of solvent carefully under reduced pressure (0 °C bath, 50 mmHg) to give the volatile chloride **32**, which was taken up in 2.0 mL of Et_2O and used in the next step without further purification.

Sodium (50 mg, 2.174 mmol) was added to the ethereal solution of chloride **32** under argon. The reaction mixture was stirred under reflux for 5 h. The reaction was quenched carefully by the addition of ethanol (0.20 mL) and then water (2 mL). The resulting mixture was extracted with ether (3 × 5 mL), and the combined organics were washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography to give alcohol **33** (64 mg, 71% yield from **31**) as a colorless oil: R_f 0.50 (33% Et_2O in hexane); IR (film) 3410 (br), 2947, 2871, 1451, 1336, 1089, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (m, 1H), 2.48 (br t, J = 14.0 Hz, 1H), 2.06 (m, 1H), 1.94−1.35 (m, 12H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 124.6, 81.2, 47.2, 41.9, 37.1, 30.4, 27.5, 27.2, 26.2, 19.6; LRMS (EI) *m*/*z* 166 (M^+, 13), 149 (23), 148 (100), 133 (75), 119 (74), 105 (79), 91 (60); HRMS (EI) *m*/*z* calcd for $C_{11}H_{18}O$ 166.1358, found 166.1363.

Acknowledgment. The work described in this paper was supported by a grant from the Research Grants Council of Hong Kong Special Administrative Region, China (Project No. HKU 7081/01P), The University of Hong Kong Hung Hing Ying Physical Sciences Research Fund, and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01). B.C. thanks the University of Hong Kong for an exchange scholarship. R.Y.Y.K. thanks the University of Hong Kong for a Swire Fellowship. We thank Dr. Yunhong Zheng for technical assistance.

Supporting Information Available: Experimental procedures and characterization for compounds **19**, **20**, and **25**; ^1H and ^{13}C NMR spectra for compounds **3a,b**, **4**, **7**, **8**, **10**−**18**, **21**−**26, 29**−**31**, **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026399M