JOC The Journal of Organic Chemistry

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Total Synthesis of the Macrocyclic *N*-Methyl Enamides Palmyrolide A and 2*S*-Sanctolide A

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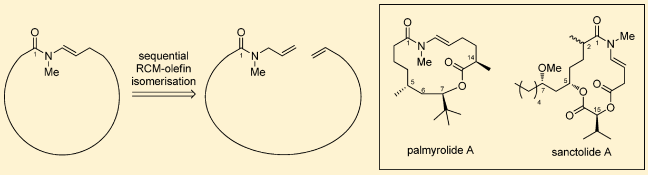
Supporting Information

ABSTRACT: Full details of the total syntheses of the initially reported and revised structures of the neuroprotective agent palmyrolide A are reported. The key macrocyclization step was achieved using a sequential ring-closing metathesis/olefin isomerization reaction. Furthermore, the total synthesis of the related macrolide (2*S*)-sanctolide A is reported. The synthesis used key elements from the synthesis of palmyrolide A, including the RCM/olefin isomerization sequence. The synthetic work described herein serves to facilitate the assignment of stereochemistry of the natural product sanctolide A and demonstrates the utility of this approach for the synthesis of macrocyclic tertiary enamide natural products.



INTRODUCTION

Marine cyanobacterial assemblies are a rich source of unique natural products which exhibit a broad range of biological activity.[1] One interesting family of macrocyclic secondary metabolites that possess the rare *N*-methyl enamide moiety (Figure 1) is comprised of the laingolides (**1**−**3**),[2] madangolide (**4**),[2a] palmyrolide A (**5a**),[3] and sanctolide A (**6**).[4] The most interesting biological activity exhibited by the macrocyclic *N*-methyl enamides has been reported for the neuroprotective agent palmyrolide A (**5a**).[3] While biological evaluation of the remaining members of the group is limited, their close structural similarity to palmyrolide A (**5a**) renders them attractive candidates for further investigation.

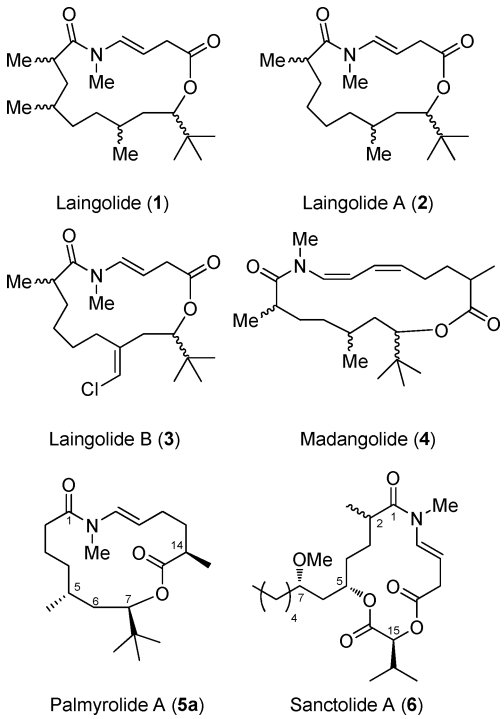


Figure 1. Macrocyclic *N*-methyl enamide natural products.

Palmyrolide A (**5a**) was isolated from *Leptotyngbya* cf. sp. and *Oscillatoria* sp. by Gerwick and co-workers as part of a drug discovery program.[3] The natural product **5** displayed promising neuroprotective properties as a potent inhibitor of calcium oscillations in murine cerebrocortical neurons and potent sodium channel blocking in neuroblastoma cells.[3] Initially, the structure of palmyrolide A (**5b**,**c**) was assigned on the basis of an analysis of detailed one- and two-dimensional ^{1}H and ^{13}C NMR experiments; however, the absolute stereochemistry of the natural product could not be fully confirmed. The absolute stereochemistry of a single stereocenter, C-14, was assigned as *R* and the relative stereochemical arrangement for the remaining C-5/C-7 system was proposed to be *syn*. However, distinction between the two possible 5,7-*syn* diastereomers (5*R*,7*S*,14*R*)-**5b** and (5*S*,7*R*,14*R*)-**5c** was not possible at this stage (Figure 2).[3] More recently, the C-5/C-7 *syn* stereochemistry was revised on the basis of an elegant total synthesis by Maio and co-workers, who established that the natural product actually possessed *anti*-configured C-5/C-7 stereochemistry (5*R*,7*R*,14*R*-**5a**; Figure 2).[5] This reassignment has since been confirmed not only by our own synthesis[6] but also by those reported by Sudhakar et al.[7] and Reddy et al.,[8] both of which achieved macrocyclization by formation of the *N*-methyl enamide through intramolecular *N*-alkylation of an amide, in a manner similar to that reported by Maio et al.[5]

Received: September 29, 2014
Published: November 4, 2014

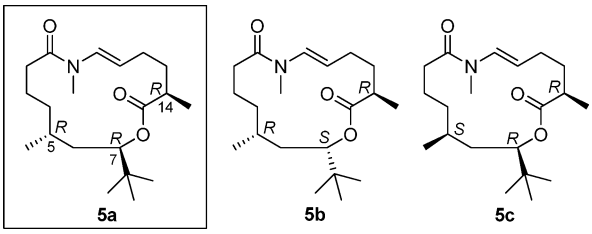
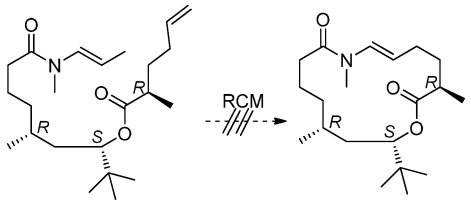


Figure 2. Initially proposed (**5b**,**c**)[3] and revised (**5a**)[5] structures of palmyrolide A.

Our synthetic studies toward palmyrolide A (**5a**) commenced prior to publication of the work reported by Maio et al.[5] and was initially focused on the synthesis of the reported C-5/C-7 *syn* isomer (5*R*,7*S*,14*R*-**5b**).[3] Our original approach to palmyrolide A was directed toward executing the ring-closing metathesis (RCM)[9] of acyclic enamide/olefin **7a** as the final step (Scheme 1). Unfortunately, despite investigation of a range of RCM conditions, no macrocyclization of enamide **7a** was observed.

Scheme 1. Originally Planned Final Synthetic Transformation



Pleasingly, by reconsidering the order of the late-stage transformations and modification of the ring-closing precursor, we were able to achieve the successful synthesis of both initially reported 14*R*-5,7-*syn* diastereomers (**5b**,**c**) and the natural product palmyrolide A (**5a**).[6] A key element in the altered synthetic approach involved RCM as the penultimate step and subsequent olefin isomerization of the macrocyclic product to form the important *N*-methyl enamide functionality. Having completed the synthesis of palmyrolide A (**5**), we became interested in applying a similar strategy to the synthesis of related *N*-methyl enamide natural products. Interestingly, to date no syntheses have been reported for any of the other macrocyclic *N*-methyl enamide natural products.

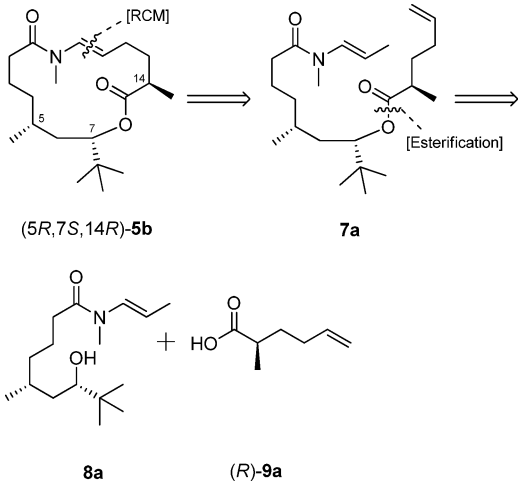
Kang and co-workers recently reported the isolation of sanctolide A (**6**),[4] from a culture of cyanobacteria *Oscillatoria* sancta. During determination of the structure of sanctolide A (**6**)[4] the absolute configuration at C-5, C-7 ,and C-15 was established by Mosher ester analysis and chiral HPLC. However, the absolute stereochemistry at C-2 was not determined. Two diastereomers were therefore possible for the structure of natural sanctolide A (**6**).[4] The synthesis of sanctolide A (**6**) was thus envisaged to be achieved using an analogous sequence for macrocyclization and enamide formation, thus enabling determination of the stereochemistry of the unassigned stereocenter at C-2.

Herein, we report the full details of the synthesis of two diastereomers of palmyrolide A, namely (5*R*,7*S*,14*R*)-**5b** and (5*R*,7*S*,14*S*)-**5d** (*ent*-**5c**) together with the revised natural structure (5*R*,7*R*,14*R*)-**5a** of palmyrolide A. Application of the RCM/olefin isomerization strategy to the synthesis of the related 2*S*-sanctolide A (**6a**) is also reported, thereby further demonstrating the utility of this strategy to access *N*-methyl enamide containing natural products.

RESULTS AND DISCUSSION

Initial Retrosynthetic Analysis of Palmyrolide A (5). During the initial stage of our work, the absolute C-5/C-7 stereochemistry of palmyrolide A (**5**) remained unknown. Our synthetic route was therefore designed to be amenable to the synthesis of both *syn*-C-5/C-7 diastereomers (5*R*,7*S*,14*R*)-**5b** and (5*S*,7*R*,14*R*)-**5c**. Hence, our retrosynthesis arbitrarily focused on production of the 5*R*,7*S* isomer **5b** (Scheme 2).

Scheme 2. Initially Proposed Retrosynthetic Analysis of Palmyrolide A (5b)



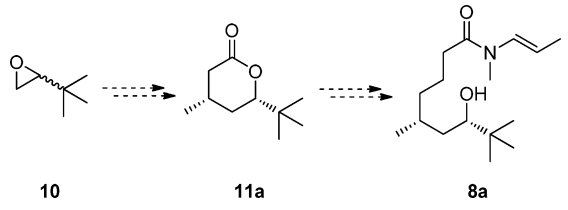
The first disconnection in our retrosynthetic analysis of palmyrolide A (**5b**) involved construction of the enamide double bond. The key macrocyclization/enamide formation step would be achieved via macrocyclic ring-closing metathesis (RCM) of enamide **7a**. A similar RCM strategy utilizing disubstituted acyclic enamide olefins has been reported by Evano et al.[9b] in their synthesis of a number of macrocyclic secondary enamides. Further disconnection of the ester bond in the RCM precursor **7a** gave two key fragments: namely, alcohol **8a** and the known acid **9a**. For the purpose of assigning the absolute stereochemistry of the natural product it was deemed most efficient to prepare a pair of C-14 epimers using a single *syn*-5*R*,7*S* diastereomer of alcohol **8a**, which should produce the natural product or its enantiomer. This would require both the (*R*)-**9a** and (*S*)-**9b** enantiomers of the carboxylic acid coupling partner, which could be accessed in a few linear steps.[10] Comparison of the NMR signals and optical rotation measurements of the synthetic palmyrolide macrocycles thus prepared with those of the natural material would then allow assignment of the absolute stereochemistry of the natural product.

Synthesis of Initially Targeted Enamide Coupling Partner 8a. Our initial efforts for the synthesis of palmyrolide A (**5b**) focused on the synthesis of enamide intermediate **8a** from commercially available racemic *tert*-butyl epoxide **10** (Scheme 3). Synthesis of this coupling partner involved installation of the two stereocenters at C-5 and C-7 in the natural product.

Synthesis of palmyrolide A (**5a**) began with installation of the correct stereochemistry at what would become C-7 in the

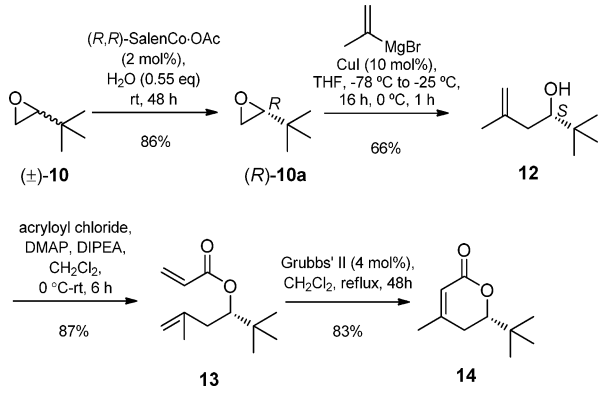
dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179−11193

Scheme 3. Proposed Synthesis of Enamide 8a



final target compound **5a** (Scheme 4). High enantiopurity of the key starting material **10a** was essential, as the steric bulk of

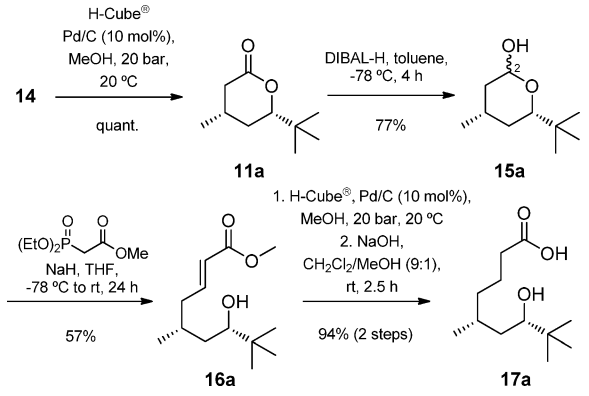
Scheme 4. Synthesis of Dihydropyranone 14



the *tert*-butyl group would later be used to direct the installation of a second stereocenter. The standard procedure[11] for hydrolytic kinetic resolution (HKR) was used to effect resolution of racemic epoxide **10**. Successful resolution was confirmed by comparison of the specific rotation value recorded for **10a** to that reported in the literature ($[\alpha]_D^{20}$ = −13.9° (*c* 2.1, PhH); lit. $[\alpha]_D^{20}$ = −14.6° (*c* 2.2, PhH)[12]). Unsaturated alcohol **12** was then prepared by ring opening of epoxide **10a** with the commercially available prop-1-en-2-ylmagnesium bromide. Alcohol **12** was next reacted with acryloyl chloride to afford ester **13** in 87% yield. RCM of diene **13** proceeded smoothly in the presence of Grubbs' second-generation catalyst (4 mol %) to deliver dihydropyranone **14**.

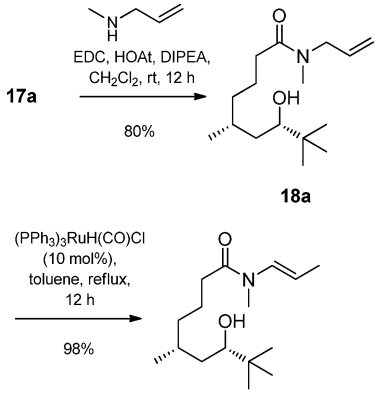
The next step in our synthetic plan required installation of the second stereocenter. Diastereomeric control was of paramount importance to access the desired *syn* stereochemistry in the final product. Hydrogenation of unsaturated lactone **14** was performed using an H-cube flow reactor fitted with a 10 mol% palladium on carbon catalyst cartridge (Scheme 5). Gratifyingly, this process gave the desired lactone product **11a** as a single diastereomer in quantitative yield, as confirmed by comparison of the ^{1}H NMR data to literature values for the related *anti* diastereomer,[13] as well as 2D homonuclear NOESY NMR techniques. Reduction of lactone **11a** with DIBAL-H[14] delivered the desired lactol **15a** as a 3:2 mixture of C-2 epimers, as determined by the presence of two sets of diastereomeric signals in both the ^{1}H NMR and ^{13}C NMR spectra. HWE olefination[15] of the open chain aldehyde tautomer of lactol **15a** with commercially available methyl diethylphosphonoacetate afforded alkene **16a**. Hydrogenation of olefin **16a** was achieved using an H-cube flow reactor under the same conditions as previous hydrogenation to effect smooth transformation to the saturated product in quantitative yield. Saponification of the methyl ester was completed under standard conditions to afford carboxylic acid **17a** in an excellent 94% yield over two steps.

Scheme 5. Synthesis of Carboxylic Acid 17a



Coupling of carboxylic acid **17a** with commercially available *N*-methylallylamine was conducted employing water-soluble carbodiimide EDC, producing amide **18a** in 80% yield (Scheme 6). Isomerization of *N*-methylallylamide **18a** was next achieved using $(PPh_3)_3RuH(CO)Cl$, affording *N*-methylenamide **8a** in 98% yield and completing the first desired coupling partner.

Scheme 6. Synthesis of Enamide Coupling Partner 8a



Synthesis of Initially Targeted Acid Coupling Partner 9a. Synthesis of the desired acid **9a** has been previously reported employing the chiral oxazolidinone auxiliary **19c**.[10] In an attempt to establish the optimal conditions required to prepare acid **9a**, three oxazolidinone auxiliaries **19a−c** were investigated in the present work. Under conditions previously reported by Wu et al.,[10] 1,4-conjugate allylation of *α,β*-unsaturated *N*-acyl oxazolidinone compounds **19a−c** was carried out, using titanium tetrachloride as the Lewis acid and employing two different allyl metal reagents (Table 1).[16]

Although addition of allyl metal reagents to unsaturated oxazolidinones **19a−c** proceeded well, none of the conditions used provided the desired *syn* diastereomers **20a−c** exclusively (entries 1−5, Table 1). However, diastereomers **20a−c** and **21a−c** could be easily separated using flash chromatography to deliver the single desired *syn* diastereomer **20** in >99% de, as indicated by ^{1}H NMR. Use of allyltributylstannane (entries 1, 3, and 5, Table 1) resulted in a higher level of reactivity in comparison to that when allyltrimethylsilane was used (entries 2 and 4, Table 1), and in all cases better diastereoselectivity resulted. Reaction of (4*S*)-3-methacryloyl-4-phenyl-2-oxazolidinone (**19c**) with allyltributylstannane afforded the best yield

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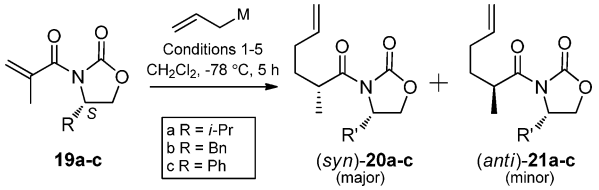
Table 1. Lewis Acid Promoted Allylation of Amide 19a−c

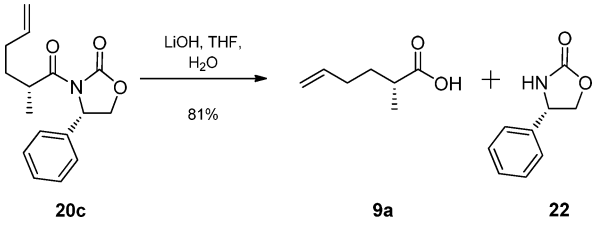


entry	R	Lewis acid	allylmetal reagent	yield (%)	de (%)
1	*i*-Pr	$TiCl_4$	(allyl)$SnBu_3$	49	29
2	Bn	$TiCl_4$	(allyl)$SiMe_3$	73	11
3	Bn	$TiCl_4$	(allyl)$SnBu_3$	76	28
4	Ph	$TiCl_4$	(allyl)$SiMe_3$	46	10
5	Ph	$TiCl_4$	(allyl)$SnBu_3$	98	76

and the best diastereoselectivity (**20c**:**21c** 87%:11%, entry 5, Table 1).

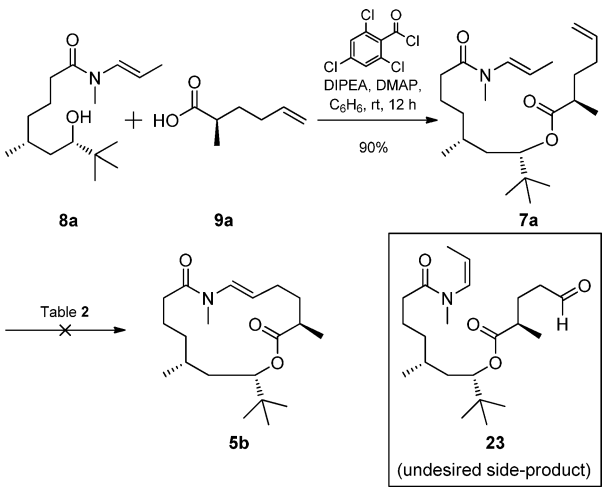
With the enantiopure *syn*-oxazolidinone allylation product **20c** in hand, the final step in the synthesis of the chiral acid (*R*)-methyl-5-hexenoic acid (**9a**) required removal of the chiral auxiliary **22** via saponification. Pleasingly, the oxazolidinone **22** was removed under basic conditions to provide the desired chiral acid **9a** in high yield (Scheme 7).

Scheme 7. Saponification of Oxazolidinone Auxiliary 20c



Esterification and Attempted Macrocyclization via RCM. Construction of the sterically hindered ester bond was next undertaken by employing Yamaguchi's reagent (2,4,6-trichlorobenzoyl chloride).[13a] Pleasingly, union of the acid **9a** and the alcohol **8a** was completed successfully, delivering the desired ester **7a** in 90% yield (Scheme 8).

Scheme 8. Esterification and Attempted RCM To Produce Macrocyclic Enamide 5b



With the key enamide ring closing precursor **7a** in hand, we turned out attention to the final step of the planned synthesis of (5*R*,7*S*,14*R*)-palmyrolide A (**5b**, Table 2). As shown in Table 2, RCM of enamide **7a** was attempted with a range of conditions employing different catalysts, concentrations, temperatures, solvents and reaction times. Disappointingly, none of these conditions produced the desired RCM product **5b** and only the starting diene **7a** was recovered after each attempt (entries 1−6, Table 2).

A lack of reactivity observed with Grubbs' catalysts has been associated with formation of stable five- and six-membered cyclic chelates.[9a] By competing for coordination at the carbonyl oxygen, addition of a Lewis acid can effectively reduce or minimize this intramolecular ruthenium carbene chelation.[17] A selection of Lewis acids were therefore screened as additives to effect the RCM of enamide **7a** (entries 7−9, Table 2). Although reaction was observed in all cases, the isolated compound was not the desired cyclization product **5b** but rather aldehyde **23**, as identified by NMR and HR-ESI-MS analysis. This result may be rationalized by internal coordination of the ester carbonyl group to the ruthenium, leading to intermediate **24** (Scheme 9). Subsequent addition of water then results in the formation of the observed aldehyde **23** via intermediate **25**.[9a]

Modified Retrosynthetic Analysis of Palmyrolide A (5). Ultimately, when the final RCM step could not be conducted to access (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) as planned, a modified synthetic strategy was required. It was envisioned that RCM of a terminal monosubstituted olefin could be employed as a penultimate step that precedes olefin isomerization taking place within the macrocyclic system. Adopting this strategy, the synthesis of alcohol coupling partner **18a** remains the same; however, a final olefin isomerization of the RCM product (**26a**) is required (Scheme 10). The shorter acid coupling partner **28a** is thus required to produce the 15-membered ring upon RCM. Synthesis of a single *syn* alcohol coupling partner **18a** followed by esterification with both enantiomers of acid **28** provides access to the two epimeric RCM precursors (5*R*,7*S*,14*R*)-**27a** and (5*R*,7*S*,14*S*)-**27b**, which would enable elucidation of the natural stereochemistry of palmyrolide A (**5**).

Synthesis of the Required Acid Coupling Partner 28a. Using the synthetic method described by Myers et al.,[18] (*R*)-2-methylpent-4-enoic acid (**28a**) was synthesized in three steps from (+)-pseudoephedrine in excellent yield (84% over three steps) and enantiopurity.

Synthesis of Originally Reported *syn* Palmyrolide A (5b). With both coupling partners, acid **28a** and alcohol **18a** in hand, attention turned to formation of the required ester **27a** (Scheme 11). Pleasingly, esterification using 2,4,6-trichlorobenzoyl chloride afforded ester **27a** in 89% yield. RCM of diene **27a** was initially attempted using Grubbs' second-generation catalyst. Gratifyingly, no undesired side reactions were observed and the desired macrocycle **26a** was the sole product with a small amount of starting diene **27a** being recovered. $(PPh_3)_3RuH(CO)Cl$ was next added to a solution of macrocycle **26a**, and the resulting mixture was heated at reflux over 24 h. Pleasingly, complete consumption of the starting material **26a** took place and (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) was afforded in 88% yield.

The total synthesis of (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) was executed in an overall yield of 7.3% with the longest linear sequence of 13 steps from commercially available racemic *tert*-butyl oxirane **10**. Disappointingly, comparison of the ^{1}H NMR

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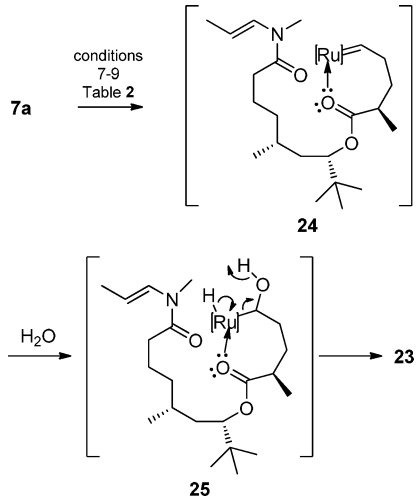
Table 2. Attempted RCM for the Synthesis of Macrocycle (5*R*,7*S*,14*R*)-Palmyrolide A (5b)

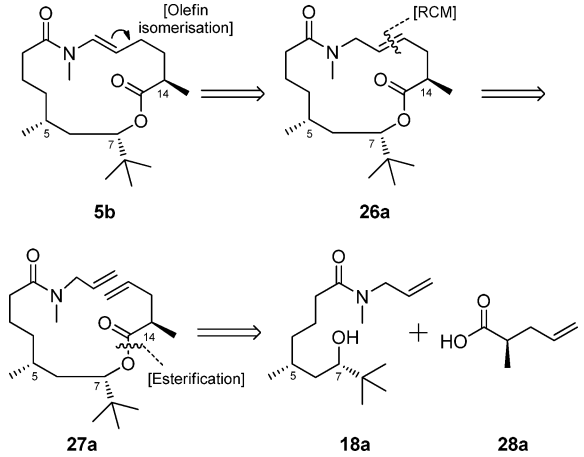
entry	catalyst	cat. loading (mol %)	solvent	temp (°C)	Lewis acid	amt of aldehyde **23** (%)	amt of returned enamide **7a** (%)
1	GII[a]	10	CH_2Cl_2	45			100
2	GII	20	CH_2Cl_2	45			97
3	GII	20	1,2-DCE	90			95
4	GII	30	1,2-DCE	90			87
5	GII	20	toluene	120			92
6	HGII[b]	20	1,2-DCE	90			98
7	GII	10	1,2-DCE	90	$Ti(OiPr)_4$	50	36
8	GII	10	1,2-DCE	90	$(C_6H_{11})_2BCl$	98	
9	GII	10	1,2-DCE	90	LiCl	30	62

[a]GII = Grubbs' second-generation catalyst. [b]HGII = Hoveyda–Grubbs' second-generation catalyst.

Scheme 9. Proposed Mechanism for the Formation of Observed Aldehyde 23



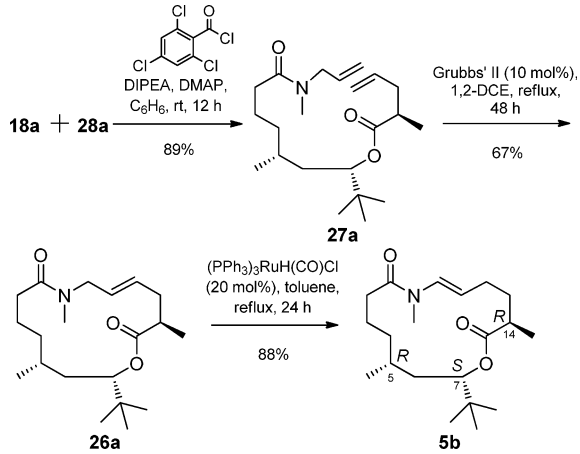
Scheme 10. Modified Retrosynthetic Analysis of (5*R*,7*S*,14*R*)-Palmyrolide A (5b)



data showed that the synthetic (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) did not match the isolated natural product. The recorded optical rotation ($[\alpha]_D^{19}$ = −42.6° (*c* 0.97, $CHCl_3$)) for synthetic (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) also significantly differed from that reported for the natural product ($[\alpha]_D^{24}$ = −29° (*c* 0.9, $CHCl_3$)).[3]

With the original assignment of stereochemistry at C-14 as *R*,[3] the above successful synthesis of (5*R*,7*S*,14*R*)-palmyrolide A (**5b**) suggested that the alternative 5,7-*syn* diastereomer

Scheme 11. Completion of the Synthesis of (5*R*,7*S*,14*R*)-Palmyrolide A (5b)



(5*S*,7*R*,14*R*)-palmyrolide A (**5c**) was in fact the natural product. However, with the 5*R*,7*S* alcohol **18a** already in hand, together with a robust method for the synthesis of (*S*)-2-methylpent-4-enoic acid (**28b**), synthesis of the enantiomeric (5*R*,7*S*,14*S*)-palmyrolide A (**5d**) presented the more expedient route to confirm the absolute stereochemistry of the natural product.[3]

Synthesis of (5*R*,7*S*,14*S*)-Palmyrolide A (5d). The acid coupling partner **28b** required was next prepared in good yield (63% over three steps) and enantiopurity, starting from (−)-pseudoephedrine using a method analogous to that employed for the synthesis of enantiomeric *R* acid **28a**.

With the required *S* acid **28b** and alcohol **18a** in hand, attention turned to the final coupling/RCM/isomerization steps (Scheme 12). Formation of ester **27b** by coupling of acid **28b** and alcohol **18a** was achieved employing 2,4,6-trichlorobenzoyl chloride. Subsequent RCM of diene **27b** using Grubbs' II catalyst afforded macrocycle **26b**. Finally, reacting macrocyclic amide **26b** under reflux in the presence of $(PPh_3)_3RuH(CO)Cl$ completed the synthesis of the desired enamide (5*R*,7*S*,14*S*)-palmyrolide A (**5d**) in good yield (48% over three steps).

Successful synthesis of (5*R*,7*S*,14*S*)-palmyrolide A (**5d**) provided spectroscopic data for comparison with the data reported for natural palmyrolide A.[3] To our surprise, comparison of the ^1H and ^{13}C NMR data of this second *syn* diastereomer (5*R*,7*S*,14*S*)-**5d** also did not match the data for natural palmyrolide A. If the initial relative C-5/C-7 *syn* assignment were correct, the NMR data for one of the synthetic palmyrolide A C-5/C-7 *syn* diastereomers (5*R*,7*S*,14*R*)-**5b** or

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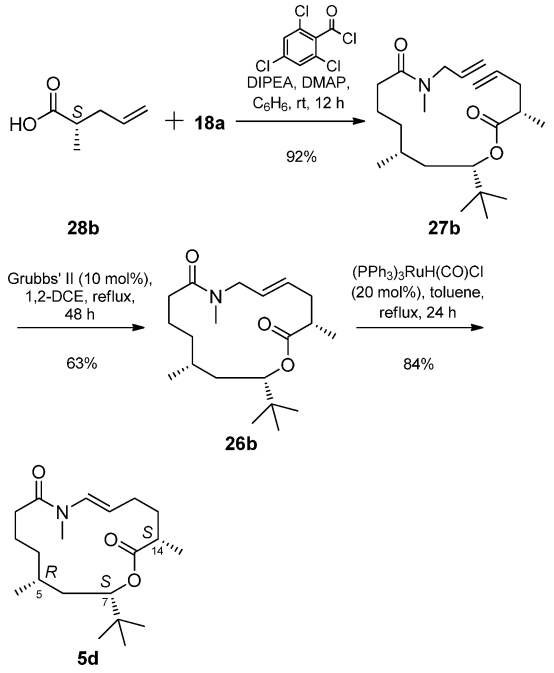
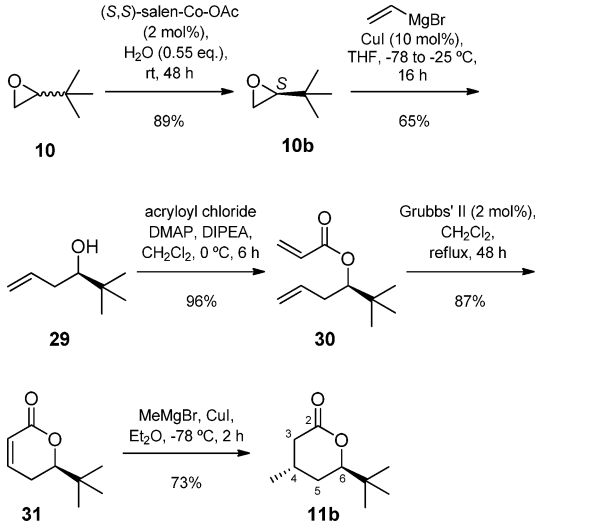
Scheme 12. Synthesis of (5*R*,7*S*,14*S*)-Palmyrolide A (5d)



Scheme 13. Synthesis of Anti Lactone 11b



(5*R*,7*S*,14*S*)-**5d** should have matched the natural product. The discrepancies observed in the NMR spectra recorded for both of the synthesized palmyrolide diastereomers (5*R*,7*S*,14*R*)-**5b** and (5*R*,7*S*,14*S*)-**5d** indicated that the original *syn* assignment proposed for the relative C-5/C-7 stereochemistry of the natural product was incorrect.

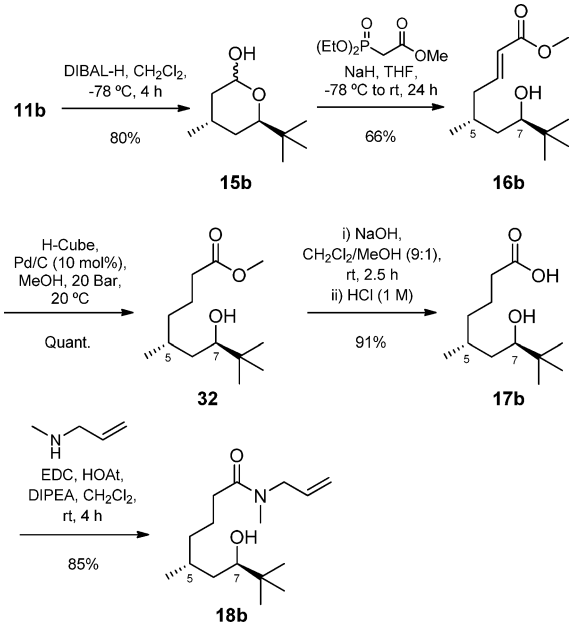
Coincidentally, at this stage the first total synthesis of (5*R*,7*R*,14*R*)-palmyrolide A (**5a**) was reported by Maio et al.[5] Their synthesis established the assignment of the absolute stereochemistry of the natural product to be (5*R*,7*R*,14*R*)-palmyrolide A (**5a**, Figure 1). In light of this new information, we next focused our own investigations toward the synthesis of the natural C-5/C-7 *anti* isomer of palmyrolide A (**5a**).

Synthesis of the Natural Product (5*R*,7*R*,14*R*)-Palmyrolide A (5a) from *anti* Lactone 11b. With a view to accessing a lactone intermediate possessing the required *anti* configuration (**11b**, cf. **11a**), we now considered the directing ability of the bulky C-6 *tert*-butyl substituent to control installation of the methyl substituent at C-3 of the lactone using a 1,4-conjugate addition to dihydropyranone **31** (Scheme 13).[16,19] It was satisfying to find that the dihydropyranone **31** required for synthesis of our targeted *anti* lactone **11b** could be produced from *tert*-butyl epoxide **10** using a method analogous to that employed for the synthesis of *syn*-lactone **11a**. HKR of racemic epoxide **10** provided the desired *S* enantiomer **10b**, thereby installing the stereochemistry at what would become C-7 of the natural product **5a**. The resultant *S* epoxide **10b** was opened with vinylmagnesium bromide to give secondary alcohol **29**. Esterification of alcohol **29** with acryloyl chloride produced the ring-closing precursor **30** in good yield. Finally, RCM was achieved using Grubbs' II catalyst, generating the desired dihydropyranone intermediate **31** in a short and high-yielding sequence.

With intermediate **31** in hand, attention turned to the key 1,4-conjugate addition to install the second stereocenter with the desired *anti* relationship. Dihydropyranone **31** underwent conjugate addition of methylmagnesium bromide to give the desired *anti*-configured lactone **11b** as a single diastereomer. The relative stereochemistry of lactone **11b** was determined by comparison with the reported ^{1}H and ^{13}C NMR spectral data for the enantiomeric lactone.[13a,19]

With *anti* lactone **11b** in hand, we were confident that synthesis of the natural 5*R*,7*R*,14*R* isomer of palmyrolide A (**5a**) could be achieved using the methodology previously optimized for the synthesis of the *syn* diastereomers **5b**,**d**. DIBAL-H reduction of lactone **11b** afforded lactol **15b**, which was subjected to Horner–Wadsworth–Emmons olefination with methyl diethylphosphonoacetate to afford olefin **16b** (Scheme 14). Reduction of the olefin by hydrogenation using our previously established hydrogenation conditions gave the saturated product **32** in quantitative yield. Saponification of the methyl ester **32** under basic conditions proceeded smoothly to yield carboxylic acid **17b**. Finally, amidation was completed

Scheme 14. Synthesis of Required Alcohol Coupling Partner 18b



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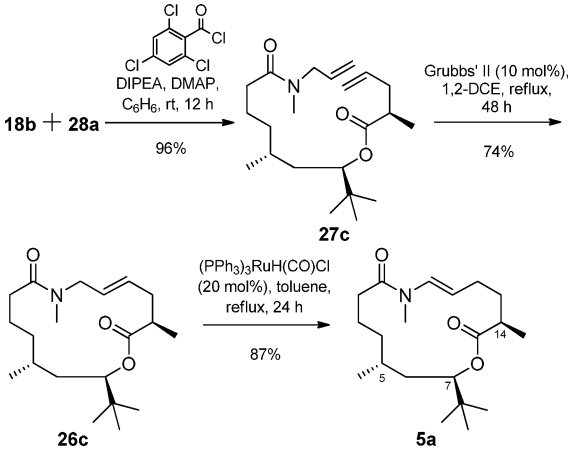
using EDC and *N*-methylallylamine, delivering the desired *N*-methyl, *N*-allyl tertiary amide **18b** in good overall yield.

Having completed the synthesis of the amide **18b**, the planned coupling/RCM/isomerization sequence to access palmyrolide A (**5a**, Scheme 15) was next undertaken.

Scheme 15. Synthesis of the Natural Product (5*R*,7*R*,14*R*)-Palmyrolide A (5a)



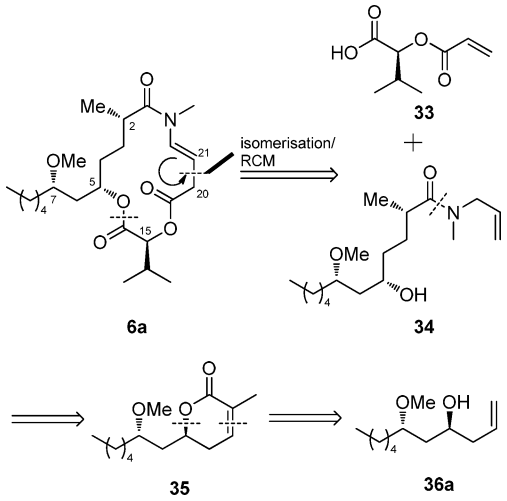
Esterification of chiral acid **28a** and alcohol **18b** was achieved using 2,4,6-trichlorobenzoyl chloride to form the desired ring-closing precursor **27c**. RCM of diene **27c** using Grubbs' II catalyst afforded the desired macrocycle **26c** in 74% yield. The final isomerization proceeded as planned using $(PPh_3)_3RuH(CO)Cl$, delivering natural (5*R*,7*R*,14*R*)-palmyrolide A (**5a**). The optical rotation measured for our synthetic palmyrolide A (**5a**) ($[\alpha]_D^{19}$ = −27.4° (*c* 0.56, $CHCl_3$)) showed very good agreement with that reported for both the natural product ($[\alpha]_D^{23}$ = −29° (*c* 0.9, $CHCl_3$))[3] and the reported synthetic ($[\alpha]_D$ = −27° (*c* 0.86, $CHCl_3$))[5b] (5*R*,7*R*,14*R*)-palmyrolide A (**5a**). The NMR data recorded for our synthetic (5*R*,7*R*,14*R*)-palmyrolide A (**5a**) was also in excellent agreement with those reported for the natural product.[3]

The second total synthesis of the natural product (5*R*,7*R*,14*R*)-palmyrolide A (**5a**)[6] reported herein was achieved in 9% overall yield and 13 linear steps from commercially available *tert*-butyl epoxide **10**, comparing favorably to the previously reported synthesis (7%, 10 steps).[5]

Retrosynthetic Analysis of Sanctolide A (6). Having successfully completed the synthesis of palmyrolide A (**5**), our attention next turned to the synthesis of the related *N*-methyl enamide natural product sanctolide A (**6**). Retrosynthetic analysis of sanctolide A (**6**) focused on application of the same RCM/isomerization protocol for macrocyclization and construction of the important *N*-methyl enamide moiety (Scheme 16). Disconnection of the lactone gave two fragments: acid **33** and alcohol **34**. With ambiguity surrounding the stereochemistry at C-2, synthesis of either of the possible C-2 epimers of sanctolide A (**6**) would enable assignment of the natural stereochemistry at C-2. It was postulated that the *S* configuration at C-2 of sanctolide A (**6a**) could be accessed exclusively by stereoselective hydrogenation of dihydropyranone **35**. Access to the required dihydropyranone **35** was expected to be achievable from the known alcohol **36a** using an esterification/RCM strategy.

Synthesis of Alcohol 36a via Allylation of Hexanal (37). Starting from commercially available hexanal (**37**) an

Scheme 16. Retrosynthetic Analysis of 2*S*-Sanctolide A (6a)



attempt was made to construct the desired alcohol **36a** using a series of asymmetric allylation reactions (Table 3).

Our initial attempt to synthesize alcohol **36a** involved using the conditions reported by Marco et al.[20] (entry 1, Table 3). Allylation of hexanal (**37**) with (+)-diisopinocampheylchloroborane ((+)-Ipc_2BCl) and allylmagnesium bromide produced the *S* alcohol **38**, installing the first required stereocenter. The optical rotation of alcohol **38** compared well to previously reported data for *S* alcohol **38**.[21] Protection of alcohol **38** using methyl iodide furnished methyl ether **39**.

With alkene **39** in hand, an aldehyde intermediate was afforded via ozonolysis, thus facilitating a second asymmetric allylation (Table 3). The second allylation was undertaken on the crude aldehyde intermediate using similar conditions (entry 1, Table 3). Disappointingly, though the reaction provided alcohol **36** in 60% yield, the ^1H NMR spectrum indicated the formation of an inseparable mixture of *anti* and *syn* diastereomers of alcohols **36a**,**b**. In our hands, the best diastereomeric ratio achieved via double Brown allylation of hexanal (**37**) with Ipc_2BCl was ∼4:1 (*anti*:*syn*), as determined by integration of the diastereomeric methoxy groups in the ^1H NMR spectrum. An alternative method for the asymmetric synthesis of target alcohol **36a** was therefore sought (entries 2−4, Table 3).

A range of conditions were investigated for both asymmetric allylation steps in an attempt to produce the desired *anti* alcohol **36a**. An alternate borane reagent (Ipc_2BOMe, entry 2, Table 3), an allyl titanium catalyst (entry 3), and an indium-mediated allylation (entry 4) were all employed, to varying levels of success. Disappointingly, none of the conditions attempted were able to produce exclusively the desired *anti* alcohol **36a**; hence, alternative methods to access this key intermediate were required.

Alternative Approach to the Synthesis of Intermediate Alcohol 36a. Ultimately, successful synthesis of alcohol **36a** began with the *m*-CPBA-mediated epoxidation of hept-1-ene (**40**) to give the HKR precursor epoxide **41** (Scheme 17). Kinetic resolution with catalytic (*S*,*S*)-salenCo^{III}-OAc provided access to a single enantiomer of epoxide **41a**. Pleasingly, the optical rotation measured ($[\alpha]_D^{20}$ = −11.9° (*c* 0.75, $CHCl_3$)) showed very good correlation with the value reported by Schneider et al.[22] ($[\alpha]_D^{20}$ = −9.5° (*c* 1.0, $CHCl_3$)). Epoxide **41a** was next opened with vinylmagnesium bromide to produce the

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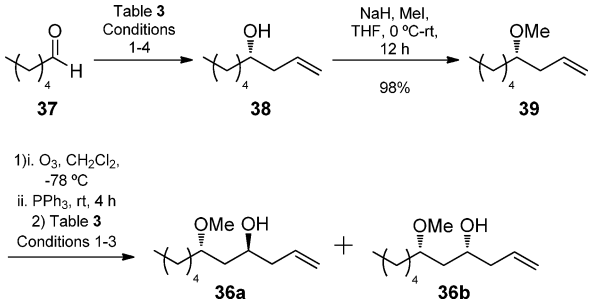
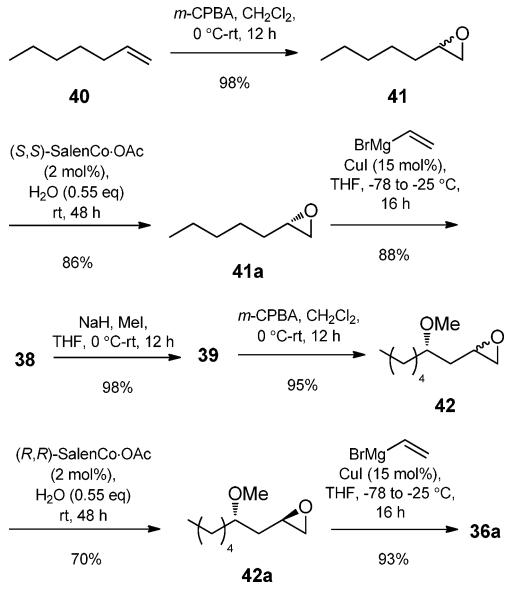
Table 3. Attempted Synthesis of Alcohol 36a using a Double Asymmetric Allylation Strategy



entry	chiral reagent	allyl reagent	yield of **38** (%)	**38** $[\alpha]_D$,[a] deg	yield of **36** (%)	dr *anti*:*syn*
1	Ipc_2BCl	allylMgBr	92	−8.3 (*c* 1.1, $CHCl_3$)	60	4:1
2	Ipc_2BOMe	allylMgBr	80	−6.6 (*c* 1.4, $CHCl_3$)	68	1:1
3	$[Ti(i\text{-}PrO)(BINOL)]_2O$	$allylSnBu_3$	91	−5.3 (*c* 1.0, $CHCl_3$)	82	3:2
4	In^0/2-amino-1,2-diphenylethanol	allylBr	95	−3.8 (*c* 1.1, $CHCl_3$)		

[a] lit. $[\alpha]_D^{21} = -9.0°$ (*c* 1.5, $CHCl_3$).

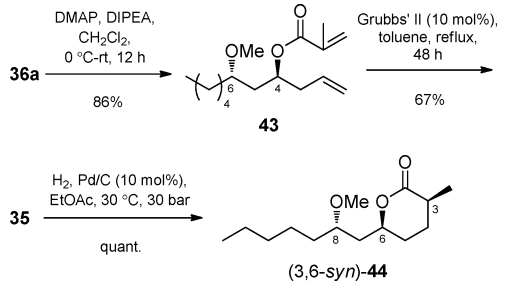
Scheme 17. Synthesis of *anti* Alcohol Intermediate 36a via Epoxide HKR



desired homoallylic alcohol **38** in 88% yield. Alcohol **38** was subsequently treated with methyl iodide to give methyl ether **39**. With methyl ether **39** in hand, the epoxidation/HKR/Grignard ring-opening process was repeated to produce homoallylic alcohol **36a** (Scheme 17). Epoxidation was carried out using *m*-CPBA to deliver a 50:50 diastereomeric mixture of epoxides **42**. HKR of epoxides **42** using catalytic (*R*,*R*)-salenCo^{III}-OAc delivered the *anti* diastereomer epoxide **42a**. Gratifyingly, comparison of the ^1H and ^{13}C NMR spectra for the resolved product **42a** with that of the racemic starting mixture **42** indicated the isolation of a single diastereomer of epoxide **42a**. Clear separation for almost all signals was observed, providing an excellent indicator of the diastereomeric purity. Finally, epoxide **42a** underwent opening with vinylmagnesium bromide to deliver the desired *anti* alcohol product **36a** as a single diastereomer. The diastereoselectivity of the synthetic route and enantiopurity of the isolated product **36a** were confirmed by comparison of the NMR and optical rotation data to those reported by Marco et al.[20]

Synthesis of Intermediate Lactone 44 and Installation of Desired Stereochemistry at C-2. Having completed the synthesis of alcohol **36a**, we turned out attention to furnishing the desired lactone **44** and installation of the C-2 stereochemistry. Pleasingly, the synthesis of the required dihydropyranone intermediate **35** proceeded readily from alcohol **36a** (Scheme 18). Esterification was achieved by reaction of alcohol

Scheme 18. Synthesis of Dihydropyranone 35 and Stereoselective Hydrogenation To Produce 3,6-*syn* Lactone 44



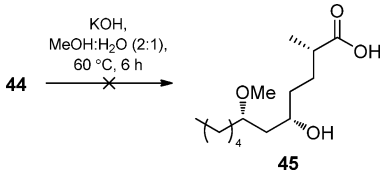
36a with freshly distilled methacryloyl chloride. The resultant RCM precursor, diene **43**, was cyclized to dihydropyranone **35** using Grubbs' II catalyst. It was predicted that if the substituent at C-6 of dihydropyranone **35** provided sufficient steric bulk to exclude approach of the palladium catalyst from one face, hydrogenation would occur exclusively from the opposite face. We were encouraged by a recent report from Yu et al.[23] which described a similar approach used in the total synthesis of the carpenter bee pheromone *syn*-2-methyl-5-hexanolide. *syn*-selective hydrogenation of dihydropyranone **35** was executed using an H-cube flow reactor fitted with a palladium on carbon (10 mol %) catalyst cartridge. Pleasingly, the ^1H NMR spectra and 2D NOESY NMR spectra of lactone **44** indicated the presence of a single 3,6-*syn* diastereomer.

Synthesis of Alcohol Coupling Partner 34. With the completion of the synthesis of lactone **44**, we were in a position to continue the synthesis of the alcohol coupling partner **34**. We had planned saponification of lactone **44** as a means of accessing the desired acid intermediate **45** (Scheme 19). However, under the basic conditions employed no trans-

dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179−11193

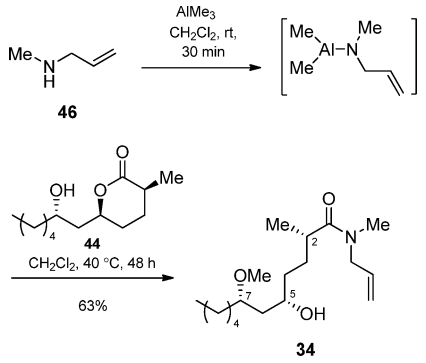
formation of lactone **44** was observed and only starting material was returned.

Scheme 19. Attempted Saponification of Lactone 44 for the Production of Acid 45



It was next thought that lactone **44** could undergo opening with an amine to form the desired amide **34** in a one-pot ring-opening/amidation reaction under the conditions reported by Kim et al.[24] (Scheme 20). Commercially available *N*-

Scheme 20. Synthesis of Alcohol Coupling Partner 34



methylallylamine (**46**) was treated with trimethylaluminum to form a dimethylaluminum amide intermediate. This reactive aluminum amide was then added to lactone **44** to deliver the desired amide **34** in 63% yield.

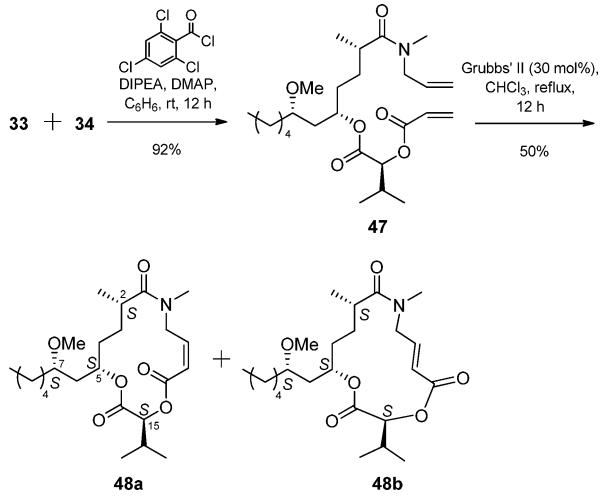
Synthesis of Acid Coupling Partner 33. With the desired alcohol coupling partner **34** in hand, three of the four stereocenters were set, and our attention turned to synthesis of the complementary acid coupling partner **33**. Hydroxydeamination of L-valine[25] and subsequent esterification with acryloyl chloride under standard conditions afforded the desired acid coupling partner **33**.

Completion of the Synthesis of 2*S*-Sanctolide A (6a). With the successful completion of both the alcohol **34** and acid **33** coupling partners, the final steps in the synthesis of (2*S*,5*S*,7*S*,15*S*)-sanctolide A (**6a**) could be attempted. The remainder of the proposed synthetic route was based on transformations used for the synthesis of palmyrolide A (**5a**): namely, esterification, macrocyclic RCM, and olefin isomerization.

Coupling of acid **33** and alcohol **34** was first achieved using 2,4,6-trichlorobenzoyl chloride to produce the desired diene ring-closing precursor **47** in 92% yield (Scheme 21). Macrocyclic RCM was next completed in the presence of Grubbs' II catalyst, giving the closed-ring product **48** in 50% yield.

Inspection of the ^{1}H NMR spectrum of RCM product **48** revealed that a 1:1 mixture of (*Z*)-**48a** and (*E*)-**48b** unsaturated macrocycles had formed. This conclusion was reached by the observation of complex splitting patterns for the resonances assigned to the protons in close proximity to the carbon–carbon double bond. The complexity of these resonances made

Scheme 21. RCM for the Synthesis of Macrocyclic Structures (*Z*)-48a and (*E*)-48b



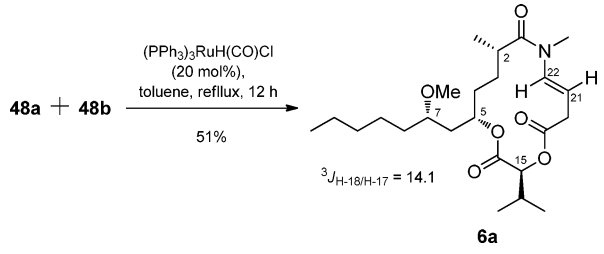
detailed assignment of the ^{1}H NMR spectrum difficult; however, the success of the ring-closing step was tentatively confirmed on the basis of the recorded mass for the isolated product (HRMS-ESI *m*/*z* [M + Na]$^+$ calcd for [$C_{24}H_{41}NO_6$ + Na]$^+$, 462.2826; found, 462.2812). No further characterization was attempted, and the inseparable mixture was subjected to the final isomerization reaction.

It was expected that, during the final isomerization step, the carbon–carbon π bond would adopt the most stable conjugated position. In the ring-closed products (*Z*)-**48a** and (*E*)-**48b**, the target double bond is in conjugation with the neighboring ester functionality. However, migration of the double bond into conjugation with the amide is predicted to provide a lower energy alternative, on the basis of computer energy modeling of the (*Z*)-vinylic lactone **48a** and enamide **6a** compounds using the Spartan '08 modeling software. By employing a conformational search with geometry minimization followed by a semiempirical, ab initio Hartree–Fock point energy calculations, a relative energy difference of 14.86 kJ/mol was estimated in favor of the enamide compound, sanctolide A (**6a**).

Further confirmation of successful ring-closing metathesis was obtained through completion of the final planned olefin isomerization step, which afforded a single *trans* isomer of enamide **6a** by treatment of the mixture of (*Z*)-**48a** and (*E*)-**48b** olefins with catalytic $(PPh_3)_3RuH(CO)Cl$ (Scheme 22).

Inspection of the ^{1}H NMR spectrum of enamide **6a** showed no evidence for the presence of any other diastereomers, and the *trans* arrangement of the carbon–carbon double bond was indicated by the large vicinal $^3J_{H,H}$ coupling value of 14.1 Hz for

Scheme 22. Final Double Bond Isomerization in the Synthesis of 2*S*-Sanctolide A (6a)



dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179–11193

H-22. Disappointingly, comparison of the ^{1}H and ^{13}C NMR data to those reported for the natural product[4] displayed a small discrepancy in the NMR spectrum recorded. The HRMS of our synthetic compound **6a** (m/z [M + Na]$^+$ calcd for [$C_{24}H_{41}NO_6$ + Na]$^+$, 462.2832; found, 462.2810) was also an excellent match to the predicted mass for the targeted compound **6**. However, a large difference in optical rotation between synthetic (2*S*,5*S*,7*S*,15*S*)-sanctolide A (**6a**) ($[\alpha]_D^{22}$ = +38.6° (*c* 0.3, MeOH)) and the reported value ($[\alpha]_D^{25}$ = −41° (*c* 0.1, MeOH))[4] coupled with the small differences in the ^{1}H NMR spectra suggested that the synthetic (2*S*,5*S*,7*S*,15*S*)-sanctolide A (**6a**) produced in the present work is in fact a diastereomer of the natural product.

CONCLUSION

In conclusion, we have completed the total synthesis of two 5,7-*syn*-configured analogues of palmyrolide A (**5b,d**) that refutes the initially proposed structural assignment of this neuroprotective natural product. Furthermore, we have completed a complementary synthesis of the revised structure of (5*R*,7*R*,14*R*)-palmyrolide A (**5a**) that further confirms the reassignment of palmyrolide A by Maio and co-workers.[3] The synthesis of (5*R*,7*R*,14*R*)-palmyrolide A (**5a**) reported herein proceeded in 9% overall yield (13 steps), which compares favorably with the previous synthesis (7%, 10 steps).[3] Using the same strategy developed for the synthesis of palmyrolide A (**5**), we have also successfully completed the first total synthesis of the 2*S* diastereomer of sanctolide A (**6a**) in 13 linear steps and 4% overall yield from known epoxide **41a**. Completion of the synthesis of (2*S*)-sanctolide A (**6a**) with defined stereochemistry provides useful information about the stereochemical configuration of the natural product. A modified synthesis aimed at producing the 3,6-*anti* diastereomer of intermediate lactone **44** would enable confirmation of the proposed stereochemistry of the natural product sanctolide A (**6**). The synthetic approach reported herein encompassing an esterification/RCM/isomerization sequence demonstrates that this strategy is a useful method that could also be applied to the synthesis of the related natural products such as the laingolides[3−5] and madangolide.[4]

EXPERIMENTAL SECTION

General Procedures. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 and MeOH were freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as the visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230−400 mesh) was used for flash chromatography. Preparatory TLC was carried out on 500 μm, 20 × 20 cm silica gel thin-layer chromatography plates. NMR spectra were recorded at room temperature in $CDCl_3$, CD_3OD, $(CD_3)_2CO$, C_6D_6, or $(CD_3)SO$ solutions on either a spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) on the δ scale, and coupling constants, *J*, are in hertz (Hz). Multiplicities are reported as "s" (singlet), "br s" (broard singlet), "d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), and "m" (multiplet). Where distinct from those due to the major rotamer, resonances due to the minor rotamers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, and NOESY spectra. Infrared (IR) spectra were recorded as thin films on a composite of zinc selenide and diamond crystal on a FT-IR system transform spectrometer. Melting points are uncorrected. High-resolution mass spectra (HRMS) were obtained using a spectrometer operating at a nominal accelerating voltage of 70 eV or on a TOF-Q mass spectrometer.

Compounds 5a,b,d, 10−18, and 26−32. Experimental procedures for the preparation of compounds **5a,b,d**, **10−18**, and **26−32** as well as data pertaining to the characterization and purity of each of the compounds has been reported previously.[6]

(5*R*,7*S*)-7-Hydroxy-*N*,5,8,8-tetramethyl-*N*-((*E*)-prop-1-en-1-yl)nonanamide (8a). To a solution of amide **18a** (20.0 mg, 0.075 mmol) in toluene (5.0 mL) was added $(PPh_3)_3RuH(CO)Cl$ (7.0 mg, 0.008 mmol, 10 mol %), and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and filtered through Celite, rinsing with dichloromethane (3 × 5 mL). Solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/1) as eluent to give the title compound **8a** (19.6 mg, 0.07 mmol, 98%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (s, 9 H, ^{t}Bu), 0.89 (d, *J* = 6.4 Hz, 3 H, Me), 1.16−1.39 (m, 4 H, 2 × CH_2, H-4 + H-6), 1.60−1.75 (m, 3 H, CH + CH_2, H-5 + H-3), 1.72 (dd, *J* = 1.2, 6.4 Hz, 3 H, Me), 2.38−2.44 (m, 2 H, CH_2, H-2), 3.06 (s, 3 H, NMe), 3.28 (d, *J* = 10.0 Hz, 1 H, CH, H-7), 4.96−5.06 (m, 1 H, CH, H-10), 6.64 (dd, *J* = 1.6, 14 Hz, 1 H, CH, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.5 (Me, C-11), 19.0 (Me, C-12), 22.4 (CH_2, C-3), 25.7 (^{t}Bu, 3 × Me), 29.4 (CH, C-5), 29.9 (NMe), 34.0 (CH_2, C-2), 34.9 (C, C-9), 38.0 (CH_2, C-4), 38.7 (CH_2, C-6), 77.2 (CH, C-7), 106.7 (CH, C-10), 129.0 (CH, C-9). C═O not observed; $[\alpha]_D^{20}$ = −20.6° (*c* 0.68, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2953, 2923, 2853, 1956, 1782, 1644, 1461, 1435, 1395, 1377, 1264, 1085, 739; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{16}H_{31}NO_2$ + Na]$^+$ 292.2247, found 292.2257.

(*S*)-4-Isopropyl-3-((*R*)-2-methylhex-5-enoyl)oxazolidin-2-one (20a) and (*S*)-4-Isopropyl-3-((*S*)-2-methylhex-5-enoyl)-oxazolidin-2-one (21a). To a solution of (*S*)-4-isopropyl-3-methacryloyloxazolidin-2-one (**19a**; 50 mg, 0.5 mmol) in dichloromethane (2.0 mL) at −78 °C was added titanium tetrachloride (0.17 mL, 1.5 mmol), and the reaction mixture was stirred for 30 min. Tributylallylstannane (0.48 mL, 1.5 mmol) was added, and the reaction mixture was stirred at −78 °C for a further 5 h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous phase extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude products were purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/2) as eluent to give the title compounds (*S*,*R*)-**20a** (47.0 mg, 0.20 mmol, 39.2%) and (*S*,*S*)-**21a** (12.0 mg, 0.05 mmol, 10.0%) as colorless oils. Data for **20a** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (d, *J* = 6.8 Hz, 3 H, Me), 0.90 (d, *J* = 7.2 Hz, 3 H, Me), 1.14 (d, *J* = 6.8 Hz, 3 H, Me, H-14), 1.49 (dt, *J* = 7.2, 14.0 Hz, 1 H, CH of CH_2, H-10a), 1.83−1.92 (m, 1 H, CH of CH_2, H-10b), 2.08 (dt, *J* = 7.2, 7.6 Hz, 2 H, CH_2, H-11), 2.30−2.38 (m, 1 H, CH, H-6), 3.78 (q, *J* = 6.8 Hz, 1 H, CH, H-9), 4.17 (dd, *J* = 2.8, 8.8 Hz, 1 H, CH of CH_2, H-5a), 4.25 (t, *J* = 9.2 Hz, 1 H, CH of CH_2, H-5b), 4.45 (dt, *J* = 3.6, 8.4 Hz, 1 H, CH, H-4), 4.93−5.03 (m, 2 H, CH_2, H-13), 5.74−5.84 (m, 1 H, CH, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.6 (Me), 16.5 (Me, C-14), 17.9 (Me), 28.4 (CH, C-6), 31.2 (CH_2, C-11), 33.1 (CH_2, C-10), 37.0 (CH, C-9), 58.4 (CH, C-4), 63.1 (CH_2, C-5), 114.9 (CH_2, C-13), 137.9 (CH, C-12), 153.6 (C═O, C-2), 176.9 (C═O, C-8); $[\alpha]_D^{20}$ = +48.9° (*c* 0.90, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2963, 2934, 2875, 1775, 1697, 1384, 1372, 1299, 1234, 1199, 1119, 1056, 991, 910, 773, 689; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{13}H_{21}NO_3$ + Na]$^+$, 262.1414, found 262.1404. Data for **21a** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (d, *J* = 6.8, 3 H, Me), 0.93 (d, *J* = 7.2 Hz, 3 H, Me), 1.21 (d, *J* = 7.2 Hz, 3 H, Me, H-14), 1.43−1.52 (m, 1 H, CH of CH_2, H-10a), 1.81−1.90 (m, 1 H, CH of CH_2, H-10b), 2.03−2.10 (m, 2 H, CH_2, H-11), 2.31−2.39 (m, 1 H, CH, H-6), 3.75 (dt, *J* = 6.8, 7.2 Hz, 1 H, CH, H-9), 4.19 (dd, *J* = 3.2,

dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179−11193

9.2 Hz, 1 H, CH of CH_2, H-5a), 4.25 (t, J = 9.2 Hz, 1 H, CH of CH_2, H-5b), 4.44 (ddd, J = 3.2, 4.0, 8.0 Hz, 1 H, CH, H-4), 4.92−5.03 (m, 2 H, CH_2, H-13), 5.73−5.83 (m, 1 H, CH, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.6 (Me), 14.7 (Me), 17.5 (Me, C-14), 28.5 (CH, C-6), 31.5 (CH_2, C-10), 32.2 (CH_2, C-11), 37.2 (CH, C-9), 58.4 (CH, C-4), 63.2 (CH_2, C-5), 114.8 (CH_2, C-13), 138.1 (CH, C-12), 153.6 (C═O, C-2), 177.0 (C═O, C-8); $[\alpha]_D^{20}$ = +54.8° (c 1.20, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2958, 2924, 2873, 1779, 1699, 1458, 1384, 1299, 1238, 1200, 1057, 992, 964, 910, 773, 701; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{13}H_{21}NO_3 + Na]^+$ 262.1414, found 262.1401.

(*S*)-4-Benzyl-3-((*R*)-2-methylhex-5-enoyl)oxazolidin-2-one (20b) and (*S*)-4-Benzyl-3-((*S*)-2-methylhex-5-enoyl)oxazolidin-2-one (21b). To a stirred solution of (*S*)-4-benzyl-3-methacryloyloxazolidin-2-one (**19b**; 50.0 mg, 0.2 mmol) in dichloromethane (2.0 mL) at −78 °C was added titanium tetrachloride (0.07 mL, 0.6 mmol), and the resultant mixture was stirred for 30 min. Tributylallylstannane (0.2 mL, 0.6 mmol) was added, and the reaction mixture was stirred at −78 °C for a further 5 h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and the aqueous phase extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude products were purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/2) as eluent to give the title compounds (*S*,*R*)-**20b** (29.9 mg, 0.10 mmol, 52.0%) and (*S*,*S*)-**21b** (14.3 mg, 0.05 mmol, 24.0%) as colorless oils. Data for **20b** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.18 (d, J = 6.8 Hz, 3 H, Me), 1.49−1.58 (m, 1 H, CH of CH_2, H-15a), 1.87−1.96 (m, 1 H, CH of CH_2, H-15b), 2.10−2.17 (m, 2 H, CH_2, H-16), 2.72 (dd, J = 10.0, 13.2 Hz, 1 H, CH of CH_2, H-6a), 3.32 (dd, J = 3.2, 13.2 Hz, 1 H, CH of CH_2, H-6b), 3.77 (q, J = 6.8 Hz, 1 H, CH, H-14), 4.16 (d, J = 3.2 Hz, 1 H, CH of CH_2, H-5a), 4.17 (dd, J = 3.2, 9.2 Hz, 1 H, CH of CH_2, H-5b), 4.65−4.71 (m, 1 H, CH, H-4), 4.96−5.07 (m, 2 H, CH_2, H-18), 5.78−5.89 (m, 1 H, CH, H-17), 7.20−7.36 (m, 5 H, 5 × CH, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.8 (Me), 31.3 (CH_2, C-16), 32.8 (CH_2, C-15), 37.1 (CH, C-14), 38.0 (CH_2, C-6), 55.4 (CH, C-4), 66.0 (CH_2, C-5), 115.0 (CH_2, C-18), 127.3 (Ar-CH), 128.9 (2 × Ar-CH), 129.4 (2 × Ar-CH), 135.3 (C, C-7), 137.9 (CH, C-17), 153.0 (C═O, C-2), 177.0 (C═O, C-13); $[\alpha]_D^{20}$ = +33.17° (c 1.06, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2923, 1776, 1695, 1454, 1384, 1349, 1206, 1099, 971, 912, 762, 748, 701; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{17}H_{21}NO_3 + Na]^+$ 310.1414, found 310.1397. Data for **21b** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.23 (d, J = 7.2 Hz, 3 H, Me), 1.48−1.57 (m, 1 H, CH of CH_2, H-15a), 1.84−1.93 (m, 1 H, CH of CH_2, H-15b), 2.09 (q, J = 6.8 Hz, 2 H, CH_2, H-16), 2.77 (dd, J = 9.6, 13.2 Hz, 1 H, CH of CH_2, H-6a), 3.26 (dd, J = 3.2, 13.6 Hz, 1 H, CH of CH_2, H-6b), 3.69−3.78 (m, 1 H, CH, H-14), 4.15−4.23 (m, 2 H, CH_2, H-5), 4.64−4.70 (m, 1 H, CH, H-4), 4.93−5.04 (m, 2 H, CH_2, H-18), 5.74−5.84 (m, 1 H, CH, H-17), 7.20−7.35 (m, 5 H, 5 × CH, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.5 (Me), 31.5 (CH_2, C-15), 32.5 (CH_2, C-16), 37.2 (CH, C-14), 37.9 (CH_2, C-6), 55.3 (CH, C-4), 66.0 (CH_2, C-5), 114.9 (CH_2, C-18), 127.3 (Ar-CH), 128.9 (2 × Ar-CH), 129.4 (2 × Ar-CH), 135.3 (C, C-7), 138.0 (CH, C-17), 153.0 (C═O, C-2), 177.0 (C═O, C-13); spectroscopic data are consistent with those reported in the literature;[26] $[\alpha]_D^{20}$ = +70.7° (c 1.03, $CHCl_3$). Lit. $[\alpha]_D$ +78.3° (c 1.7, $CHCl_3$).[26]

(*S*)-3-((*R*)-2-Methylhex-5-enoyl)-4-phenyloxazolidin-2-one (20c) and (*S*)-3-((*S*)-2-Methylhex-5-enoyl)-4-phenyloxazolidin-2-one (21c). To a solution of (*S*)-3-methacryloyl-4-phenyloxazolidin-2-one (**19c**; 0.36 g, 1.57 mmol) in dichloromethane (20.0 mL) at −78 °C was added titanium tetrachloride (4.7 mL, 1 M, 4.7 mmol) and the reaction mixture stirred for 30 min. Tributylallylstannane (1.6 mL, 4.7 mmol) was added and the reaction was stirred at −78 °C for a further 5 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) and the aqueous phase extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography on silica gel eluting with ethyl acetate−hexanes (1:2) to give the *title compounds* (*S*,*R*)-**20c** (29.9 mg, 1.37 mmol, 87.0%) and (*S*,*S*)-**21c** (14.3 mg, 0.17 mmol, 11.0%) as colorless oils: **20c** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.15 (d, J = 6.8 Hz, 3 H, Me), 1.38−1.47 (m, 1 H, CH of CH_2, H-14a), 1.74−1.83 (m, 1 H, CH of CH_2, H-14b), 1.85−1.94 (m, 2 H, CH_2, H-15), 3.74−3.84 (m, 1 H, CH, H-13), 4.26 (dd, J = 4.0, 8.8 Hz, 1 H, CH of CH_2, H-5a), 4.68 (t, J = 8.8 Hz, 1 H, CH of CH_2, H-5b), 4.88−4.93 (m, 2 H, CH_2, H-17), 5.44 (dd, J = 4.0, 8.8 Hz, 1 H, CH, H-4), 5.66−5.76 (m, 1 H, CH, H-16), 7.27−7.41 (m, 5 H, 5 × CH, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (Me), 30.8 (CH_2, C-15), 32.7 (CH_2, C-14), 37.0 (CH, C-13), 57.7 (CH, C-4), 69.6 (CH_2, C-5), 114.8 (CH_2, C-17), 125.9 (2 × Ar-CH), 128.6 (Ar-CH), 129.0 (2 × Ar-CH), 137.8 (CH, C-16), 139.2 (C, C-6), 153.3 (C═O, C-2), 176.4 (C═O, C-12); spectroscopic data are consistent with those reported in the literature;[10] $[\alpha]_D^{20}$ = +15.7° (c 1.02, $CHCl_3$). Data for **21c** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.11 (d, J = 6.8 Hz, 3 H, Me), 1.40−1.50 (m, 1 H, CH of CH_2, H-14a), 1.79−1.89 (m, 1 H, CH of CH_2, H-14b), 2.07 (q, J = 8.0 Hz, 2 H, CH_2, H-15), 3.76 (q, J = 6.8 Hz, 1 H, CH, H-13), 4.25 (dd, J = 4.0, 8.8 Hz, 1 H, CH of CH_2, H-5a), 4.68 (t, J = 8.8 Hz, 1 H, CH of CH_2, H-5b), 4.94−5.04 (m, 2 H, CH_2, H-17), 5.43 (dd, J = 4.0, 8.8 Hz, 1 H, CH, H-4), 5.73−5.84 (m, 1 H, CH, H-16), 7.27−7.40 (m, 4 H, 4 × CH, Ar-H), 7.62 (dd, J = 3.2, 5.6 Hz, 1 H, CH, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.5 (Me), 31.5 (CH_2, C-15), 32.1 (CH_2, C-14), 37.3 (CH, C-13), 57.7 (CH, C-4), 69.8 (CH_2, C-5), 114.9 (CH_2, C-17), 125.7 (2 × Ar-CH), 128.7 (Ar-CH), 129.2 (2 × Ar-CH), 136.8 (CH, C-16), 140.3 (C, C-6), 151.5 (C═O, C-2), 1 × C═O signal not observed; $[\alpha]_D^{20}$ = +9.1° (c 1.09, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2956, 2923, 2854, 1782, 1707, 1457, 1380, 1196, 1121, 1074, 911, 763, 698; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{16}H_{19}NO_3 + Na]^+$ 296.1263, found 296.1241.

(*R*)-2-Methylhex-5-enoic Acid (9a). A solution of (*S*)-3-((*R*)-2-methylhex-5-enoyl)-4-phenyloxazolidin-2-one (**20a**; 80.0 mg, 0.29 mmol) and lithium hydroxide (18.0 mg, 0.43 mmol) in THF/water (4/1, 2.0 mL) was stirred at room temperature for 12 h. The reaction was quenched by the addition of aqueous hydrochloric acid (1 M) to bring the pH to 8.0. The reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (3 × 5 mL); the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to deliver (*S*)-4-phenyloxazolidin-2-one (**22**; 0.036 g, 77%). The remaining aqueous phase was acidified (pH 1.0) using aqueous hydrochloric acid (1 M) and extracted with dichloromethane (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound **9a** (0.03 g, 0.23 mmol, 81.0%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.19 (d, J = 7.2 Hz, 3 H, Me), 1.48−1.57 (m, 1 H, CH of CH_2, H-3a), 1.77−1.86 (m, 1 H, CH of CH_2, H-3b), 2.10 (dt, J = 7.6, 7.6 Hz, 2 H, CH_2, H-4), 2.49 (q, J = 7.2 Hz, 1 H, CH, H-2), 4.96−5.02 (m, 2 H, CH_2, H-6), 5.74−5.84 (m, 1 H, CH, H-5), OH signal not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.8 (Me), 31.2 (CH_2, C-4), 32.6 (CH_2, C-3), 38.7 (CH, C-2), 115.2 (CH_2, C-6), 137.7 (CH, C-5), 182.6 (C═O); spectroscopic data are consistent with those reported in the literature;[10] $[\alpha]_D^{20}$ = −8.7° (c 1.03, CH_2Cl_2) (lit. $[\alpha]_D^{25}$ = −8.2° (c 1.07, CH_2Cl_2)).[10]

(*R*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methyl((*E*)-prop-1-en-1-yl)-amino)-9-oxononan-3-yl 2-Methylhex-5-enoate (7a). To a solution of acid **9a** (47.5 mg, 0.54 mmol) in benzene (1.5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.09 mL, 0.54 mmol) followed by Hünig's base (0.09 mL, 0.54 mmol), alcohol **8a** (80.0 mg, 0.37 mmol), and DMAP (90.0 mg, 0.75 mmol). The reaction mixture was stirred at room temperature for 12 h, diluted with ethyl acetate (5 mL), washed with water (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/1) as eluent to give the title compound **7a** (91.3 mg, 0.25 mmol, 90% yield as a 1/1 mixture of rotamers) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (s, 9 H, ^{t}Bu), 0.90 (d, J = 6.4 Hz, 3 H, Me, H-20), 1.16 (d, J = 7.2 Hz, 3 H, Me, H-19), 1.18−1.30 (m, 4 H, CH + CH of CH_2 + CH_2, H-5 + H-6 + H-4a), 1.42−1.51 (m, 1 H, CH of CH_2, H-15a), 1.53−1.67 (m, 3 H, CH of CH_2 + CH_2, H-4b + H-7), 1.71 (dd, J = 1.6, 6.8 Hz, 3 H, Me, H-12), 1.75−1.84 (m, 1 H, CH of CH_2, H-15b), 2.06 (dt, J = 8.0, 8.0 Hz, 2 H, CH_2, H-16), 2.37 (dd, J = 7.6, 14.4 Hz, 2 H, CH_2, H-8), 2.45 (q, J = 7.2 Hz, 1 H, CH, H-

14), 3.04 (s, 3 H, NMe), 4.83 (d, J = 11.2 Hz, 1 H, CH, H-3), 4.93−5.03 (m, 3 H, CH + CH_2, H-11 + H-18), 5.72−5.82 (m, 1 H, CH, H-17), 6.60 (d, J = 15.2, 1 H, CH, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (signals for minor rotational isomer denoted with asterisks) *15.4 (Me, C-12), 15.5 (Me, C-12), 17.35 (Me, C-19), *17.43 (Me, C-19), 19.0 (Me, C-20), *19.1 (Me, C-20), 22.5 (CH_2, C-7), 26.0 (^{t}Bu, 3 × Me), 29.3 (CH, C-5), *29.4 (CH, C-5), 29.9 (NMe), 31.39 (CH_2, C-16), *31.44 (CH_2, C-16), *32.2 (CH_2, C-15), 32.8 (CH_2, C-15), 34.0 (CH_2, C-8), *34.5 (C, C-2), 34.6 (C, C-2), 36.87 (CH_2, C-4), *36.90 (CH_2, C-4), 37.9 (CH_2, C-6), 39.3 (CH, C-14), *39.4 (CH, C-14), 78.0 (CH, C-3), *105.6 (CH, C-11), 106.7 (CH, C-11), 115.0 (CH_2, C-18), *127.9 (CH, C-10), 128.9 (CH, C-10), 138.0 (CH, C-17), *171.0 (C═O, C-9), 171.3 (C═O, C-9), 176.3 (C═O, C-13); $[\alpha]_D^{20}$ = −32.1° (c 1.06, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2959, 1726, 1676, 1651, 1461, 1415, 1395, 1376, 1263, 1172, 1126, 1084, 957; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{23}H_{41}NO_3$ + Na]$^+$ 402.2979, found 402.2976.

(*R*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methyl((*E*)-prop-1-en-1-yl)-amino)-9-oxononan-3-yl 2-Methyl-5-oxopentanoate (23). To a solution of enamide **7a** (20.0 mg, 0.053 mmol) in 1,2-dichloroethane (20 mL) was added chlorodicyclohexylborane (3.5 mg, 0.016 mmol, 30 mol %), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was heated to reflux, and a solution of Grubbs' second-generation catalyst (4.5 mg, 10 mol %) in 1,2-dichloroethane (1 mL) was added. Reflux was maintained for 48 h before the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/1) as eluent to give the title compound **23** (19.8 mg, 0.052 mmol, 98% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (s, 9 H, ^{t}Bu), 0.91 (d, J = 4.0 Hz, 3 H, Me, H-19), 1.20 (d, J = 7.2 Hz, 3 H, Me, H-18), 1.22−1.31 (m, 3 H, CH + CH_2, H-5 + H-6), 1.55−1.68 (m, 5 H, CH + 2 × CH_2, H-14 + H-4 + H-7), 1.73 (dd, J = 1.2, 6.4 Hz, 3 H, Me, H-12), 1.76−1.83 (m, 1 H, CH of CH_2, H-15a), 1.93−2.02 (m, 1 H, CH of CH_2, H-15b), 2.36−2.42 (m, 2 H, CH_2, H-16), 2.47−2.52 (m, 2 H, CH_2, H-8), 3.06 (s, 3 H, NMe), 4.85 (d, J = 10.8 Hz, 1 H, CH, H-3), 4.98−5.05 (m, 1 H, CH, H-11), 6.63 (d, J = 18.0 Hz, 1 H, CH, H-10), 9.77 (s, 1 H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.5 (Me, C-12), 17.5 (Me, C-18), 19.0 (Me, C-19), 22.6 (CH_2, C-7), 25.6 (CH_2, C-8), 26.0 (^{t}Bu, 3 × Me), 29.6 (NMe), 29.9 (CH, C-5), 34.0 (C, C-2), 34.6 (CH_2, C-4), 36.8 (CH_2, C-6), 37.8 (CH_2, C-15), 39.1 (CH, C-14), 41.6 (CH_2, C-16), 78.5 (CH, C-3), 106.7 (CH, C-11), 128.9 (CH, C-10), 171.3 (C═O, C-9), 175.6 (C═O, C-13), 201.5 (CHO); $[\alpha]_D^{20}$ = −29.6° (c 0.98, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2930, 2860, 1715, 1637, 1454, 1377, 1319, 1295, 1164, 1092, 1010, 939, 812; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{22}H_{39}NO_4$ + H]$^+$ 382.2952, found 382.2949.

(4*S*)-1-Nonen-4-ol (38). To a stirred suspension of copper iodide (0.25 g, 1.31 mmol, 15 mol %) in tetrahydrofuran (20 mL) at −78 °C was added a solution of vinylmagnesium bromide (17.5 mL, 1.0 M in THF, 17.5 mmol). (2*S*)-1,2-Epoxyheptane (**41a**; 1.00 g, 8.76 mmol) was added, and the reaction mixture was warmed to −25 °C and stirred for 16 h. The solution was warmed to 0 °C, stirred for a further 1 h, then quenched with saturated aqueous ammonium chloride (25 mL). The aqueous phase was extracted with diethyl ether (2 × 25 mL), and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/9) as eluent to give the title compound **38** (1.10 g, 7.76 mmol, 88% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (t, J = 6.8 Hz, 3 H, Me), 1.23−1.38 (m, 5 H, 2 × CH_2 + CH of CH_2, H-8 + H-7 + H-6a), 1.40−1.51 (m, 3 H, CH_2 + CH of CH_2, H-5 + H-6b), 1.60 (Br s, 1 H, OH), 2.14 (ddd, J = 7.6, 7.6, 14.0 Hz, 1 H, CH of CH_2, H-3a), 2.27−2.33 (m, 1 H, CH of CH_2, H-3b), 3.60−3.70 (m, 1 H, CH, H-4), 5.11 (s, 1 H, CH of CH_2, H-1a), 5.15 (d, J = 3.2 Hz, 1 H, CH of CH_2, H-1b), 5.78−5.88 (m, 1 H, CH, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me), 22.6 (CH_2, C-8), 25.3 (CH_2, C-6), 31.8 (CH_2, C-7), 36.8 (CH_2, C-5), 41.9 (CH_2, C-3), 70.7 (CH, C-4), 118.0 (CH_2, C-1), 134.9 (CH, C-2); spectroscopic data are consistent with those reported in the literature;[21,27] $[\alpha]_D^{19}$ = −8.28° (c 1.15, $CHCl_3$) (lit. $[\alpha]_D^{16}$ = −9.0° (c 1.5, $CHCl_3$)[21]).

(*S*)-4-Methoxynon-1-ene (39). Compound **38** was produced following the procedure outlined by De Oliveira et al.[28] to give the title compound **39** (3.04 g, 19.5 mmol, 98% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, J = 6.4 Hz, 3 H, Me), 1.22−1.41 (m, 6 H, 3 × CH_2, H-6 + H-7 + H-8), 1.43−1.50 (m, 2 H, CH_2, H-5), 2.25 (dd, J = 6.8, 6.8 Hz, 2 H, CH_2, H-3), 3.19 (m, 1 H, CH, H-4), 3.33 (s, 3 H, OMe), 5.04 (d, J = 8.4 Hz, 1 H, CH of CH_2, H-1a), 5.06 (d, J = 15.6 Hz, 1 H, CH of CH_2, H-1b), 5.76−5.86 (m, 1 H, CH, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me), 22.6 (CH_2, C-8), 24.9 (CH_2, C-6), 32.0 (CH_2, C-7), 33.3 (CH_2, C-5), 37.8 (CH_2, C-3), 56.5 (OMe), 80.5 (CH, C-4), 116.7 (CH_2, C-1), 135.0 (CH, C-2); spectroscopic data are consistent with those reported in the literature;[21] $[\alpha]_D^{19}$ = −11.7° (c 1.50, $CHCl_3$) (lit. $[\alpha]_D^{16}$ = −11.4° (c 1.0, $CHCl_3$);[20] lit. $[\alpha]_D^{16}$ −12.0° (c 1.4, $CHCl_3$)[21]).

(4*S*)-Methoxy-1,2-epoxynonane (42). To a solution of *m*-chloroperoxybenzoic acid (3.40 g, 77%, 15.0 mmol) in dichloromethane (40 mL) was added (*S*)-4-methoxynon-1-ene **39** (2.00 g, 13.0 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous sodium metabisulfite (25 mL), and the organic phase was collected and washed with saturated aqueous sodium carbonate (25 mL) and then brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound **42** (2.20 g, 11.7 mmol, 92% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (50/50 mix of diastereomers*) 0.88 (t, J = 6.8 Hz, 3 H, Me), 1.23−1.40 (m, 6 H, 3 × CH_2, H-8 + H-6 + H-7), 1.41−1.62 (m, 2 H, CH_2, H-5), 1.63−1.80 (m, 2 H, CH_2, H-3), 2.47 (dd, J = 2.4, 4.4 Hz, 1 H, CH of CH_2, H-1a), *2.48 (dd, J = 2.4, 4.4 Hz, 1 H, CH of CH_2, H-1a), 2.76 (dd, J = 5.2, 12.8 Hz, 1 H, CH of CH_2, H-1b), *2.79 (dd, J = 5.2, 12.8 Hz, 1 H, CH of CH_2, H-1b), 2.96−3.07 (m, 1 H, CH, H-2), *3.33 (s, 3 H, OMe), 3.37 (s, 3 H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (diastereotopic peaks denoted with asterisks) 14.0 (Me), 22.6 (CH_2, C-8), 24.8 (CH_2, C-6), *24.9 (CH_2, C-6), *31.95 (CH_2, C-7), 31.97 (CH_2, C-7), *33.7 (CH_2, C-5), 34.0 (CH_2, C-5), *36.3 (CH_2, C-3), 37.4 (CH_2, C-3), *46.8 (CH_2, C-1), 47.5 (CH_2, C-1), *49.5 (CH, C-2), 49.8 (CH, C-2), *56.4 (OMe), 57.0 (OMe), *78.8 (CH, C-4), 78.9 (CH, C-4); IR ν_{max} (neat)/cm^{-1} 2927, 2857, 1772, 1726, 1459, 1257, 1215, 1092, 920, 840, 751, 728; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{10}H_{20}O_2$ + Na]$^+$ 195.1356, found 195.1361.

(4*S*)-Methoxy-(2*R*)-1,2-epoxynonane (42a). Glacial acetic acid (0.54 mL, 8.5 mmol) was added dropwise to a solution of [(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino]cobalt-(II) (0.50 g, 0.83 mmol, 4 mol %) in toluene (6.8 mL); the mixture was stirred at room temperature for 2 h, and a color change from red to brown was observed. Solvent and remaining acid were removed in vacuo, and (4*S*)-methoxy-1,2-epoxynonane (**42**; 3.5 g, 20.0 mmol) was added. The reaction mixture was cooled to 0 °C, water (0.2 mL, 11.0 mmol) was added dropwise, and the mixture was warmed to room temperature and stirred for 48 h. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/9) as eluent to give the title compound **42a** (1.21 g, 7.0 mmol, 70% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, J = 6.8 Hz, 3 H, Me), 1.23−1.39 (m, 6 H, 3 × CH_2, H-6 + H-7 + H-8), 1.43−1.61 (m, 3 H, CH_2 + CH of CH_2, H-5 + H-3a), 1.70−1.78 (m, 1 H, CH of CH_2, H-3b), 2.48 (dd, J = 2.8, 5.2 Hz, 1 H, CH of CH_2, H-1a), 2.80 (dd, J = 4.0, 5.2 Hz, 1 H, CH of CH_2, H-1b), 3.02−3.08 (m, 1 H, CH, H-4), 3.34−3.40 (m, 1 H, CH, H-2), 3.38 (s, 3 H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me), 22.6 (CH_2, C-8), 24.7 (CH_2, C-6), 32.0 (CH_2, C-7), 33.9 (CH_2, C-5), 37.4 (CH_2, C-3), 47.5 (CH_2, C-1), 49.8 (CH, C-4), 56.9 (OMe), 78.9 (CH, C-2); $[\alpha]_D^{20}$ = +28.6° (c 0.57, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2929, 2859, 1729, 1459, 1257, 1092, 922, 852, 751, 673; HRMS-ESI m/z [M + Na]$^+$ calcd for [$C_{10}H_{20}O_2$ + Na]$^+$ 195.1356, found 195.1348.

(4*S*,6*S*)-6-Methoxyundec-1-en-4-ol (36a). To a stirred suspension of copper iodide (0.025 mg, 0.13 mmol, 15 mol %) in diethyl ether (1.5 mL) at −78 °C was added a solution of vinylmagnesium bromide (1.4 mL, 1.0 M in THF, 1.4 mmol). A solution of (4*S*)-methoxy-(2*R*)-1,2-epoxynonane (**42a**; 0.15 g, 0.87 mmol) in diethyl

dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179−11193

ether (1.3 mL) was added dropwise, and the reaction mixture was warmed to −25 °C and stirred for 16 h. The reaction mixture was warmed to 0 °C, stirred for a further 1 h, and then quenched with saturated aqueous ammonium chloride (5 mL). The aqueous phase was extracted with diethyl ether (2 × 5 mL), and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/9) as eluent to give the title compound **36a** (0.16 g, 0.80 mmol, 93% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (t, J = 6.8 Hz, 3 H, Me), 1.25−1.35 (m, 6 H, 3 × CH_2, H-8 + H-9 + H-10), 1.40−1.51 (m, 1 H, CH of CH_2, H-5a), 1.55−1.71 (m, 3 H, CH + CH of CH_2, H-5b + H-7), 2.24 (dt, J = 1.2, 7.2 Hz, 2 H, CH_2, H-3), 2.89 (br s, 1 H, OH), 3.37 (s, 3 H, OMe), 3.44−3.50 (m, 1 H, CH, H-6), 3.90−3.98 (m, 1 H, CH, H-4), 5.04−5.15 (m, 2 H, CH_2, H-1), 5.84 (ddt, J = 7.2, 10.4, 14.4 Hz, 1 H, CH, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me), 22.6 (CH_2, C-10), 25.0 (CH_2, C-8), 32.0 (CH_2, C-9), 33.0 (CH_2, C-7), 38.9 (CH_2, C-5), 42.2 (CH_2, C-3), 56.8 (OMe), 67.9 (CH, C-4), 79.3 (CH, C-6), 117.5 (CH_2, C-1), 135.0 (CH, C-2); spectroscopic data are consistent with those reported in the literature;[20] $[\alpha]_D^{20}$ = +29.4° (c 1.13, $CHCl_3$) (lit. $[\alpha]_D$ = +25.1° (c 1.2, $CHCl_3$)[20]).

(4*S*,6*S*)-6-Methoxyundec-1-en-4-yl Methacrylate (43). A solution of (4*S*,6*S*)-6-methoxyundec-1-en-4-ol (**36a**; 0.85 g, 4.24 mmol) in dichloromethane (25 mL) was added to DMAP (0.10 g, 20 mol %, 0.85 mmol) under an argon atmosphere. The mixture was cooled to 0 °C, Hünig's base (4.0 mL, 21.2 mmol) was added, and the reaction mixture was stirred for 1 h. Freshly distilled methacryloyl chloride (5.1 mL, 50.9 mmol) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was then cooled to 0 °C and quenched carefully with saturated aqueous sodium bicarbonate (10 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/19) as eluent to give the title compound **43** (0.98 g, 3.70 mmol, 86% yield) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, J = 6.8 Hz, 3 H, Me, H-11), 1.23−1.33 (m, 6 H, 3 × CH_2, H-8 + H-9 + H-10), 1.37−1.46 (m, 1 H, CH of CH_2, H-5a), 1.47−1.56 (m, 1 H, CH of CH_2, H-5b), 1.63−1.73 (m, 2 H, CH_2, H-7), 1.93 (dd, J = 1.2, 1.6 Hz, 3 H, Me, H-15), 2.30−2.42 (m, 2 H, CH_2, H-9), 3.09−3.19 (m, 1 H, CH, H-6), 3.28 (s, 3 H, OMe), 5.03−5.10 (m, 2 H, CH_2, H-1), 5.15−5.21 (m, 1 H, CH, H-8), 5.52 (t, J = 1.6 Hz, 1 H, CH of CH_2, H-14a), 5.71−5.81 (m, 1 H, CH, H-2), 6.08 (s, 1 H, CH of CH_2, H-14b); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me, C-11), 18.3 (Me, C-15), 22.6 (CH_2, C-10), 24.6 (CH_2, C-9), 32.0 (CH_2, C-8), 33.6 (CH_2, C-7), 36.7 (CH_2, C-5), 39.4 (CH_2, C-3), 56.9 (OMe), 71.0 (CH, C-4), 77.6 (CH, C-6), 117.8 (CH_2, C-1), 124.9 (CH_2, C-14), 133.5 (CH, C-2), 136.7 (C, C-13), 166.9 (C═O); $[\alpha]_D^{19}$ = +40.4° (c 1.04, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2929, 2860, 1715, 1638, 1453, 1377, 1318, 1294, 1164, 1093, 937, 812, 693; HRMS-ESI m/z [M + Na]$^+$ calcd for $[C_{16}H_{28}O_3 + Na]^+$ 291.1931, found 291.1920.

(*S*)-6-((*S*)-2-Methoxyheptyl)-3-methyl-5,6-dihydro-2*H*-pyran-2-one (35). To a solution of diene **43** (0.10 g, 3.7 mmol) in toluene (15 mL) at reflux was added a solution of Grubbs' second-generation catalyst (0.015 mg, 0.017 mmol, 5 mol %) in toluene (5 mL), and reflux was maintained for 24 h. A second portion of Grubbs' second-generation catalyst (0.015 mg, 5 mol %) in toluene (5 mL) was added to the reaction, and reflux was continued for 24 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/4) as eluent to give the title compound **35** (0.06 g, 2.5 mmol, 67% yield) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (t, J = 6.4 Hz, 3 H, Me, H-13), 1.24−1.34 (m, 6 H, 3 × CH_2, H-10 + H-11 + H-12), 1.37−1.47 (m, 1 H, CH of CH_2, H-9a), 1.49−1.56 (m, 1 H, CH of CH_2, H-9b), 1.61 (ddd, J = 2.8, 10.4, 14.8 Hz, 1 H, CH of CH_2, H-7a), 1.85 (ddd, J = 2.4, 9.6, 14.8 Hz, 1 H, CH of CH_2, H-7b), 1.91 (dd, J = 1.6, 3.6 Hz, 3 H, Me, H-14), 2.23−2.32 (m, 2 H, CH_2, H-5), 3.35 (s, 3 H, OMe), 3.48−3.56 (m, 1 H, CH, H-8), 4.54−4.65 (m, 1 H, CH, H-6), 6.53−6.59 (m, 1 H, CH, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.9 (Me, C-13), 17.0 (Me, C-14), 22.5 (CH_2, C-12), 24.2 (CH_2, C-10), 30.4 (CH_2, C-5), 32.0 (CH_2, C-11), 33.4 (CH_2, C-9), 40.4 (CH_2, C-7), 57.0 (OMe), 75.0 (CH, C-6), 76.3 (CH, C-8), 128.3 (C, C-3), 139.1 (CH, C-4), 166.09 (C═O); $[\alpha]_D^{19}$ = −2.36° (c 1.14, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2956, 2929, 2858, 1707, 1458, 1377, 1136, 1085, 995, 912, 866, 662; HRMS-ESI m/z [M + Na]$^+$ calcd for $[C_{14}H_{24}O_3 + Na]^+$ 263.1618, found 263.1618.

(3*S*,6*S*)-6-((*S*)-2-Methoxyheptyl)-3-methyltetrahydro-2*H*-pyran-2-one (44). A solution of dihydropyranone **34** (0.066 g, 0.27 mmol) in ethyl acetate (10 mL) was passed through an H-cube flow reactor (30 °C, at 30 bar with 10 mol % Pd/C cartridge). Additional ethyl acetate (5 mL) was passed through the apparatus, and solvent was removed in vacuo to give the title compound **44** (0.066 g, 0.27 mmol, ∼100% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (t, J = 6.4 Hz, 3 H, Me, H-13), 1.21 (d, J = 6.8 Hz, 3 H, Me, H-14), 1.24−1.37(m, 6 H, 3 × CH_2, H-10 + H-11 + H-12), 1.47−1.75 (m, 5 H, CH_2 + 3 × CH of CH_2, H-9 + H-4a + H-5a + H-7a), 1.85−1.93 (m, 1 H, CH of CH_2, H-4b), 1.94−2.06 (m, 1 H, CH of CH_2, H-7b), 2.05−2.14 (m, 1 H, CH of CH_2, H-5b), 2.56−2.69 (m, 1 H, CH, H-3), 3.34 (s, 3 H, OMe), 3.46−3.55 (m, 1 H, CH, H-8), 4.50−4.57 (m, 1 H, CH, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0 (Me, C-13), 16.1 (Me, C-14), 22.6 (CH_2, C-12), 24.3 (CH_2, C10), 25.7 (CH_2, C-11), 27.3 (CH_2, C-5), 32.1 (CH_2, C-4), 33.1 (CH, C-3), 33.4 (CH_2, C-9), 40.9 (CH_2, C-7), 57.0 (OMe), 74.8 (CH, C-8), 76.5 (CH, C-6), 176.5 (C═O); $[\alpha]_D^{20}$ = +7.9° (c 1.02, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2917, 2849, 1729, 1462, 1378, 1242, 1188, 1085, 1049, 1023, 914, 731, 646; HRMS-ESI m/z [M + Na]$^+$ calcd for $[C_{14}H_{26}O_3 + Na]^+$ 265.1774, found 265.1782.

(2*S*,5*S*,7*S*)-*N*-Allyl-5-hydroxy-7-methoxy-*N*,2-dimethyldodecanamide (34). Trimethylaluminum (0.070 mL, 2 M in toluene, 0.14 mmol) was added dropwise to a solution of *N*-methylallylamine (**46**; 0.015 mL, 0.16 mmol) in dichloromethane (0.3 mL). The mixture was stirred for 30 min and added via syringe to a solution of lactone **44** (0.020 g, 0.08 mmol) in dichloromethane (0.3 mL). The reaction mixture was heated to 40 °C and stirred for 24 h before a second aliquot of trimethylaluminum (0.070 mL, 2 M in toluene, 0.14 mmol) and *N*-methylallylamine (**46**; 0.015 mL, 0.16 mmol) in dichloromethane (0.3 mL) were added, and the reaction mixture was stirred for a further 24 h. The reaction was quenched carefully with aqueous hydrochloric acid (1 M, 2.0 mL), and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/methanol (99/1) as eluent to give the title compound **34** (0.015 g, 0.050 mmol, 63% yield, 50/50 mixture of rotamers) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.89 (t, J = 8.4 Hz, 3 H, Me, H-12), 1.11 (dd, J = 4.8, 9.2 Hz, 3 H, Me, H-13), 1.22−1.35 (m, 6 H, 3 × CH_2, H-9 + H-10 + H-11), 1.38−1.69 (m, 7 H, 3 × CH_2 + CH of CH_2, H-8 + H-6 + H-4 + H-3a), 1.74−1.92 (m, 1 H, CH of CH_2, H-3b), 2.56−2.78 (m, 1 H, CH, H-2), 2.93 (d, J = 4.8 Hz, 3 H, NMe), *2.98 (d, J = 4.8 Hz, 3 H, NMe), 3.34 (s, 3 H, OMe), 3.41−3.49 (m, 1 H, CH, H-7), 3.73−3.88 (m, 1 H, CH, H-5), 3.91−4.04 (m, 2 H, CH_2, H-15), 5.09−5.23 (m, 2 H, CH_2, H-17), 5.67−5.85 (m, 1 H, CH, H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (signals for minor rotational isomer denoted with asterisks) 14.0 (Me, C-12), 18.0 (Me, C-13), *18.6 (Me, C-13), 22.6 (CH_2, C-11), 25.1 (CH_2, C-9), 29.9 (CH_2, C-3), *30.2 (CH_2, C-3), 32.0 (CH_2, C-10), 32.9 (CH_2, C-4), *33.0 (CH_2, C-4), 33.8 (NMe), *34.7 (NMe), 35.7 (CH_2, C-8), *35.7 (CH_2, C-8), *35.9 (CH, C-2), 36.0 (CH, C-2), *39.3 (CH_2, C-6), 39.5 (CH_2, C-6), *50.2 (CH_2, C-15), 52.0 (CH_2, C-15), 56.7 (OMe), *68.0 (CH, C-5), 68.6 (CH, C-5), *79.4 (CH, C-7), 79.5 (CH, C-7), *116.6 (CH_2, C-17), 117.0 (CH_2, C-17), *133.1 (CH, C-16), 133.2 (CH, C-16), 162.3 (C═O); $[\alpha]_D^{20}$ = +20.5° (c 1.13, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3422, 2930, 1736, 1626, 1463, 1404, 1373, 1265, 1089, 924; HRMS-ESI m/z [M + Na]$^+$ calcd for $[C_{18}H_{35}NO_3 + Na]^+$ 336.2509, found 336.2521.

(*S*)-2-(Acryloyloxy)-3-methylbutanoic Acid (33). To a solution of (*S*)-2-hydroxy-3-methylbutanoic acid (**48**; 0.50 g, 4.2 mmol) in dichloromethane (25 mL) was added triethylamine (3.0 mL, 20

dx.doi.org/10.1021/jo502238r | J. Org. Chem. 2014, 79, 11179−11193

mmol), and the reaction mixture was cooled to 0 °C. Acryloyl chloride (1.0 mL, 12.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (25 mL), and the aqueous phase was washed with dichloromethane (2 × 25 mL). The aqueous layer was acidified to pH 2.0 with aqueous hydrochloric acid (1 M) and extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound **33** (0.57 g, 3.3 mmol, 79% yield) as a viscous yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.04 (d, J = 3.6 Hz, 3 H, Me), 1.07 (d, J = 3.6 Hz, 3 H, Me), 2.29−2.37 (m, 1 H, CH, H-3), 4.98 (d, J = 4.4 Hz, 1 H, CH, H-2), 5.92 (dd, J = 1.2, 10.4 Hz, 1 H, CH of CH_2, H-7a), 6.21 (dd, J = 10.4, 17.2 Hz, 1 H, CH, H-6), 6.49 (dd, J = 1.2, 17.2 Hz, 1 H, CH of CH_2, H-7b), 8.55 (br s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.1 (Me), 18.8 (Me), 30.1 (CH, C-3), 76.3 (CH, C-2), 127.5 (CH, C-6), 131.9 (CH_2, C-7), 165.7 (C═O, C-5), 175.1 (C═O, C-1); $[\alpha]_D^{20}$ = −20.8° (c 1.06, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2971, 2939, 1713, 1635, 1466, 1407, 1256, 1184, 1129, 1059, 1017, 982, 947, 810; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_8H_{12}O_4 + Na]^+$ 195.0628, found 195.0626.

(*S*)-(2*S*,5*S*,7*S*)-1-(Allyl(methyl)amino)-7-methoxy-2-methyl-1-oxododecan-5-yl-2-(acryloyloxy)-3-methylbutanoate (47). To a solution of (*S*)-2-(acryloyloxy)-3-methylbutanoic acid (**33**; 12.0 mg, 0.058 mmol) in benzene (0.1 mL) were added 2,4,6-trichlorobenzoyl chloride (11.0 μL, 0.07 mmol), Hünig's base (14.0 μL, 0.079 mmol), a solution of alcohol **34** (11.0 mg, 0.035 mmol) in benzene (0.15 mL), and DMAP (14.0 mg, 0.12 mmol), and the reaction mixture was stirred at room temperature for 6 h. The reaction was diluted with ethyl acetate (5 mL) and washed with saturated aqueous sodium bicarbonate (5 mL), hydrochloric acid (1 M, 5 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexane (1/1) as eluent to give the title compound **47** (0.015 g, 0.032 mmol, 92% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.89 (t, J = 6.8 Hz, 3 H, Me, H-12), 1.01 (d, J = 5.6 Hz, 3 H, Me), 1.05 (d, J = 5.6 Hz, 3 H, Me), 1.08 (d, J = 4.8 Hz, 3 H, Me, H-27), *1.10 (d, J = 4.8 Hz, 3 H, Me, H-27), 1.20−1.35 (m, 7 H, CH of CH_2 + 3 × CH_2, H-9 + H-10 + H-11 + H-8a), 1.35−1.46 (m, 2 H, 2 × CH of CH_2, H-8b + H-4a), 1.48−1.65 (m, 5 H, CH of CH_2 + 2 × CH_2, H-4b + H-3 + H-6), 1.69−1.78 (m, 1 H, CH, H-2), 2.23−2.32 (m, 1 H, CH, H-7), 2.56−2.77 (m, 1 H, CH, H-16), 2.92 (s, 3 H, NMe), *2.98 (s, 3 H, NMe), 3.04−3.11 (m, 1 H, CH, H-5), 3.29 (s, 3 H, OMe), 3.91−4.00 (m, 2 H, CH_2, H-23), 4.88 (dd, J = 4.0, 7.2 Hz, 1 H, CH, H-15), 5.09−5.21 (m, 2 H, CH_2, H-25), 5.68−5.83 (m, 1 H, CH, H-24), 5.89 (dd, J = 1.6, 10.4 Hz, 1 H, CH of CH_2, H-21a), 6.15−6.24 (m, 1 H, CH, H-20), 6.46 (dd, J = 1.6, 10.4 Hz, 1 H, CH of CH_2, H-21b); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (signals for minor rotational isomer denoted with asterisks) 14.0 (Me, C-12), 17.2 (Me, C-17a), 17.3 (Me, C-27), *18.0 (Me, C-27), 19.0 (Me, C-17b), 22.6 (CH_2, C-11), 24.6 (CH_2, C-9), 29.0 (CH_2, C-3), *29.4 (CH_2, C-3), 30.1 (CH, C-16), 32.0 (CH_2, C-4), *32.4 (CH_2, C-4), 32.5 (CH_2, C-10), 33.4 (CH_2, C-8), *33.9 (NMe), 34.7 (NMe), *35.3 (CH, C-2), 35.4 (CH, C-2), *39.0 (CH_2, C-6), 39.1 (CH_2, C-6), 50.2 (CH_2, C-23), *52.0 (CH_2, C-23), 56.9 (OMe), *72.2 (CH, C-5), 72.7 (CH, C-5), 77.1 (CH, C-7), 77.2 (CH, C-15), *116.5 (CH_2, C-25), 116.9 (CH_2, C-25), 127.9 (CH, C-20), 131.5 (CH_2, C-21), 133.1 (CH, C-24), *133.3 (CH, C-24), 165.6 (C═O, C-1), 169.3 (C═O, C-1), *175.9 (C═O, C-19), 176.6 (C═O, C-19); $[\alpha]_D^{20}$ = −7.1° (c 1.54, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 2970, 2940, 2881, 1715, 1635, 1466, 1407, 1372, 1183, 1129, 1111, 1058, 1017, 982, 809; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{26}H_{45}NO_6 + Na]^+$ 490.3139, found 490.3160.

(2*S*,5*S*,7*S*,15*S*)-Sanctolide A (6a). A mixture of (3*S*,11*S*,14*S*)-3-isopropyl-14-((*S*)-2-methoxyheptyl)-9,11-dimethyl-1,4-dioxa-9-azacyclotetradec-6-ene-2,5,10-trione ((*Z*)-**48a** and (*E*)-**48b**) was first prepared. A solution of Grubbs' second-generation catalyst (8.0 mg, 0.009 mmol, 30 mol %) in chloroform (2 mL) was added dropwise to a refluxing solution of diene **47** (15 mg, 0.032 mmol) in chloroform (2.5 mL). The reaction mixture was heated under reflux for 12 h, and then the mixture was filtered through a plug of silica gel, rinsing with ethyl acetate (5 mL). The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/4) as eluent to give the product as an inseparable mixture of isomers (*Z*)-**48a** and (*E*)-**48b** (7.3 mg, 0.017 mmol, 50% yield): HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{24}H_{41}NO_6 + Na]^+$ 462.2826, found 462.2812. To a solution of the olefin mixture **48** (7.3 mg, 0.017 mmol) in toluene (1 mL) at reflux was added a solution of carbonylchlorohydridotris(triphenylphosphine)ruthenium-(II) (4 mg, 20 mol %) in toluene (1 mL), and reflux was maintained for 24 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexanes (1/1) as eluent to give the title compound **6a** (3.7 mg, 0.0085 mmol, 51% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.89 (t, J = 6.6 Hz, 3 H, Me, H-12), 1.00 (d, J = 6.9 Hz, 3 H, Me, H-17), 1.03 (d, J = 6.9 Hz, 3 H, Me, H-18), 1.09 (d, J = 6.6 Hz, 3 H, Me, H-13), 1.23−1.32 (m, 6 H, 3 × CH_2, H-9 + H-10 + H-11), 1.38−1.85 (m, 8 H, 4 × CH_2, H-3, H-4, H-6, H-8), 2.32−2.43 (m, 1 H, CH, H-16), 3.01−3.07 (m, 1 H, CH, H-2), 3.09 (s, 3 H, NMe), 3.11−3.16 (m, 1 H, CH, H-7), 3.20 (dd, J = 1.8, 6.3 Hz, 2 H, CH_2, H-20), 3.29 (s, 3 H, OMe), 5.03 (d, J = 4.8 Hz, 1 H, CH, H-15), 5.11−5.22 (m, 1 H, CH, H-21), 5.25−5.32 (m, 1 H, CH, H-5), 7.17 (d, J = 14.1 Hz, CH, H-22); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.0 (Me, C-12), 16.1 (Me, C-13), 17.2 (Me, C-17a), 18.7 (Me, C-17b), 22.6 (CH_2, C-11), 24.3 (CH_2, C-10), 28.7 (CH_2, C-3), 30.1 (CH, C-16), 30.4 (CH_2, C-4), 30.6 (NMe), 32.0 (CH_2, C-9), 33.3 (CH_2, C-8), 34.9 (CH_2, C-20), 36.2 (CH, C-2), 38.5 (CH_2, C-6), 56.6 (OMe), 74.2 (CH, C-5), 77.3 (CH, C-15), 77.6 (CH, C-7), 104.7 (CH, C-21), 132.1 (CH, C-22), 169.1 (C═O, C-19), 170.3 (C═O, C-14), 175.6 (C═O, C-1); $[\alpha]_D^{22}$ = +38.6° (c 0.30, MeOH); IR ν_{max} (neat)/cm^{-1} 2973, 1686, 1459, 1415, 1365, 1249, 1168; HRMS-ESI m/z $[M + Na]^+$ calcd for $[C_{24}H_{41}NO_6 + Na]^+$: 462.2862, found 462.2810.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra of compounds **6a**−**9a**, **20**, **21**, **23**, **33**−**36**, **38**, **42**−**44**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the New Zealand Foundation for Research, Science and Technology (FRST) for financial support through the International Investment Opportunities Fund (IOFF).

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