Organic LETTERS

Letter

pubs.acs.org/OrgLett

Stereoselective Synthesis of the CDE Ring System of Antitumor Saponin Scillascilloside E-1

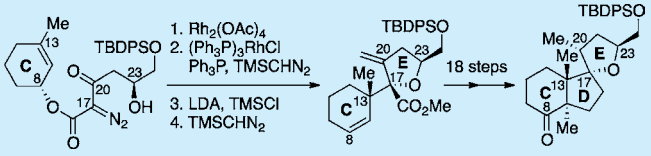
Yoshihiro Akahori,[†] Hiroyuki Yamakoshi,[†] Shunichi Hashimoto,[‡] and Seiichi Nakamura*[,†]

[†]Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

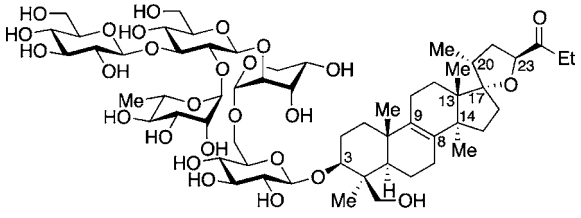
[‡]Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Supporting Information

ABSTRACT: A stereoselective synthesis of the CDE ring portion of the antitumor saponin scillascilloside E-1 has been achieved, utilizing an Ireland−Claisen rearrangement to construct the contiguous tetrasubstituted stereocenters at C13 and C17 simultaneously and intramolecular nitrile oxide cycloaddition to form the five-membered ring as key steps.



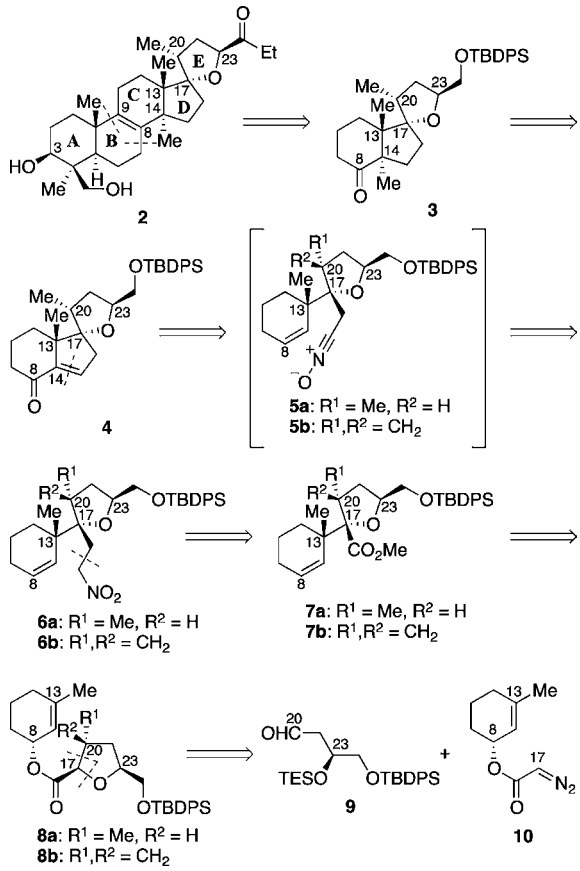
Scillascillosides are a family of eucosterol oligoglycosides isolated by Kawasaki and co-workers in 1985 from the fresh bulbs of *Scilla scilloide*, a traditional Chinese medicine.[1] These compounds were later found to exhibit remarkable cytotoxicity (ED_{50}: 1.53−3.06 nM) against several human tumor cell lines and to prolong the life span of Sarcoma 180-bearing mice.[2] Scillascilloside E-1 (**1**), the most potent antitumor agent of this family, carries a branched pentasaccharide appended to the C3 hydroxyl group of the triterpenoid aglycon, which features an oxapentacyclic system including five tetrasubstituted stereocenters. Despite the remarkable biological activities of this family, total synthesis of eucosterols has not been reported, and only the groups of Corey[3] and Kobayashi[4] accomplished total syntheses of related lanostane-type triterpenoids (lanostenol and fomitellic acid B, respectively). As part of our studies directed toward the total synthesis of the antitumor saponin **1**, we report herein a stereoselective synthesis of a CDE ring fragment of the saponin, employing an Ireland−Claisen rearrangement and intramolecular nitrile oxide cycloaddition.



Scillascilliside E-1 (**1**)

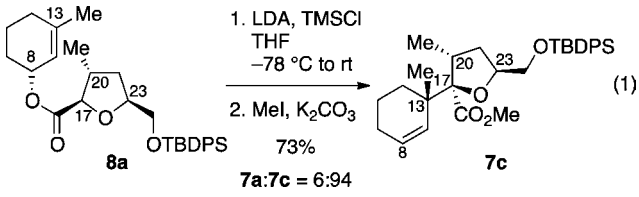
In our retrosynthetic strategy, we envisioned CDE ring fragment **3** as a suitable precursor to aglycon **2** by way of a coupling with an A ring fragment and late-stage intramolecular Heck reaction to construct the B ring (Scheme 1). Tricyclic compound **3** would be elaborated from nitro compound **6a** via enone **4** by a sequence involving an intramolecular 1,3-dipolar cycloaddition of nitrile oxide **5a**. While the contiguous tetrasubstituted stereocenters at C13 and C17 in **7a** appeared to be established in a single operation by an Ireland−Claisen rearrangement, our initial study revealed that severe steric repulsion resulting from the methyl group at C20 led to the predominant formation of an undesired stereoisomer **7c** by the

Scheme 1. Retrosynthetic Analysis of Aglycon 2



Received: March 3, 2014
Published: March 20, 2014

   dx.doi.org/10.1021/ol500657f | *Org. Lett.* 2014, 16, 2054−2057



reaction of **8a** (eq 1).[5] We therefore considered that a change in hybridization of the C20 stereocenter from sp^3 to sp^2 would minimize the repulsion and favor formation of desired isomer **7b**. Ester **8b** would be available via union of aldehyde **9** and α-diazoester **10**.

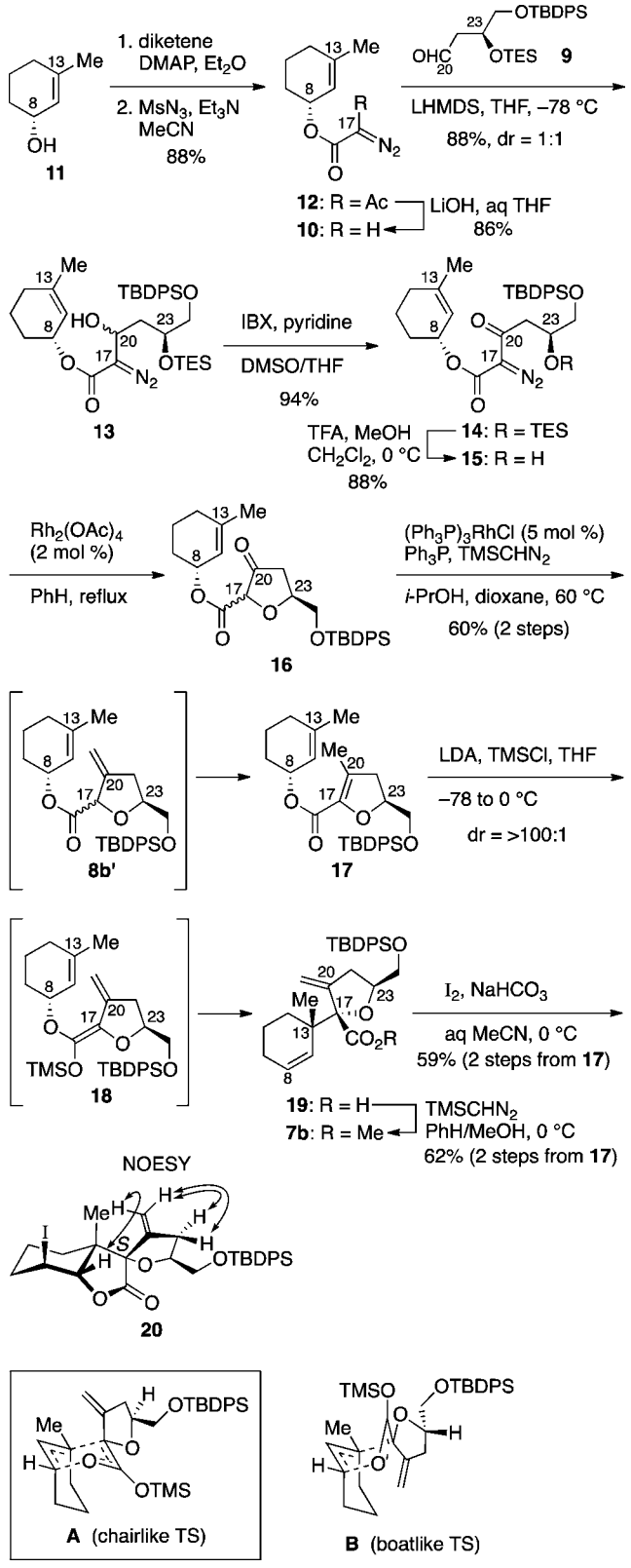
Synthesis of the rearrangement precursor **8b** was initiated with the preparation of α-diazoester **10** (Scheme 2). Acylation of alcohol **11**[5,6] with diketene in Et_2O was followed by diazo transfer with methanesulfonyl azide in MeCN to give α-diazo-β-ketoester **12** (88% yield), which upon exposure to LiOH in aqueous THF gave α-diazoester **10** in 86% yield. After the coupling of α-diazoester **10** with aldehyde **9**[7] according to the Wenkert procedure (88% yield),[8] the resultant β-hydroxyester **13** underwent oxidation with IBX[9] to afford α-diazo-β-ketoester **14** in 94% yield. Removal of the C23 TES group with TFA in $MeOH/CH_2Cl_2$ provided δ-hydroxy-α-diazoester **15** in 88% yield and set the stage for construction of the tetrahydrofuran (E) ring.

As expected from the precedent,[10] the $Rh_2(OAc)_4$-catalyzed intramolecular O–H insertion of **15** in refluxing benzene proceeded to completion within 5 min; however, the product **16** partially decomposed upon exposure to silica gel. We therefore investigated the following carbonyl olefination reaction without purification. After considerable experimentation with regard to the conversion of **16**, it was found that desired olefination could only be attained under the Lebel conditions[11] and that olefin conjugation occurred under these conditions to provide α,β-unsaturated ester **17** in 60% yield in two steps.

With substrate **17** in hand, efforts were next focused on the key Ireland–Claisen rearrangement.[12,13] The rearrangement of silyl ketene acetal **18**, generated by the reaction of **17** with LDA and TMSCl in THF at −78 °C, reached completion within 30 min even at 0 °C to furnish the rearranged product, which upon exposure to $TMSCHN_2$ gave methyl ester **7b** in 62% yield in two steps, along with a trace amount of its C17-isomer (dr = >100:1). The stereochemical assignment of major isomer **19** was established by a NOESY experiment performed on iodolactone **20** obtained by the reaction of **19** with I_2 and $NaHCO_3$ in aqueous MeCN at 0 °C. Since carboxylic acid **19** would be a product resulting from chairlike transition state **A**, it was confirmed that the selectivity of the transition state conformation is regulated by the substituent at C20.

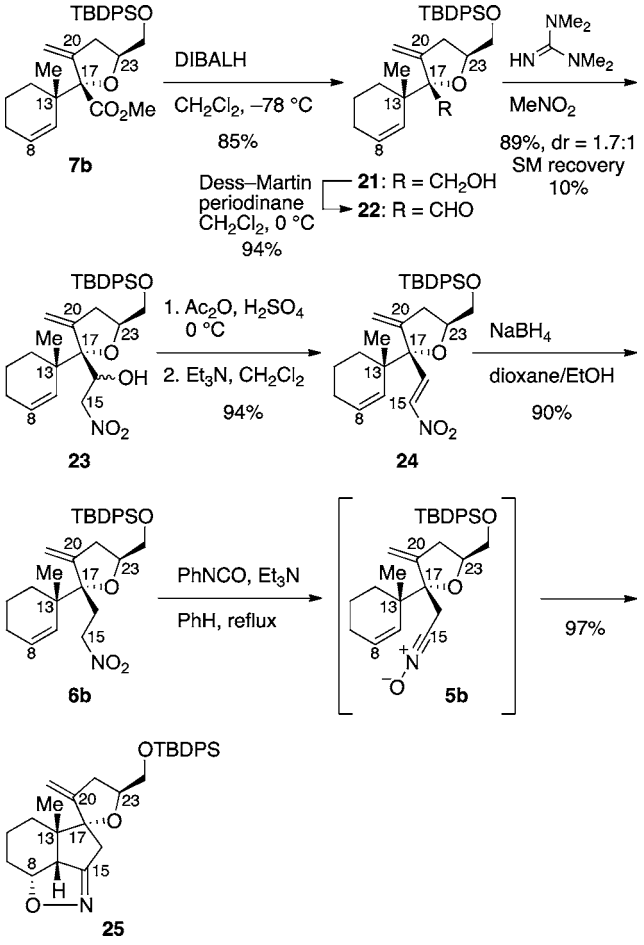
As a prelude to the one-carbon homologation, methyl ester **7b** was transformed to aldehyde **22** by a two-step sequence involving DIBALH reduction in CH_2Cl_2 at −78 °C and Dess–Martin oxidation[14] (Scheme 3). The addition of nitromethane to aldehyde **22** was best accomplished by the catalytic use of *N,N,N′,N′*-tetramethylguanidine as a base,[15] providing nitro compound **23** in 89% yield, along with recovered aldehyde **22**. Due to the propensity of **23** to undergo retro nitroaldol reaction under basic conditions, the C16 hydroxyl group in **23** was acetylated with Ac_2O in the presence of sulfuric acid at 0 °C and was removed by a two-step sequence involving elimination with Et_3N in CH_2Cl_2 and 1,4-reduction with $NaBH_4$ in dioxane/EtOH, providing cycloaddition precursor **6b** in 85% yield in three steps. As anticipated, intramolecular 1,3-dipolar cycloaddition[16,17] of nitrile oxide **5b**, generated from **6b** under Mukaiyama conditions,[18] proceeded in a stereoselective manner to give tetracyclic compound **25** in 97% yield.

Scheme 2. Construction of the Contiguous Tetrasubstituted Stereocenters by an Ireland–Claisen Rearrangement



dx.doi.org/10.1021/ol500657f | Org. Lett. 2014, 16, 2054–2057

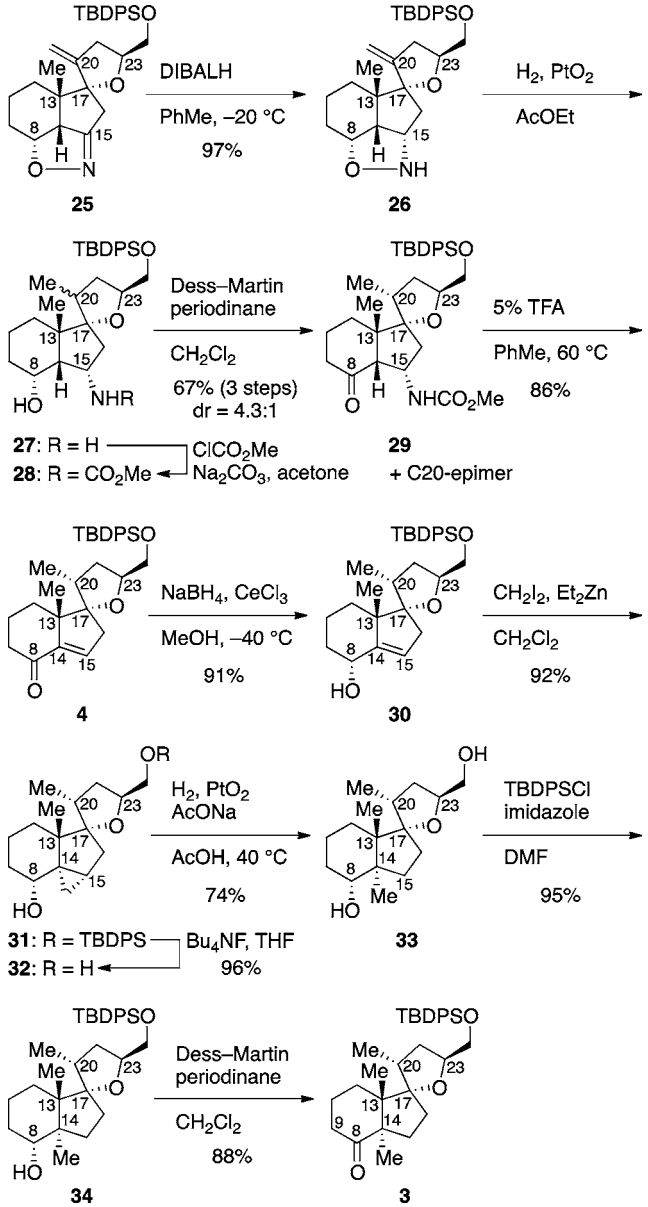
Scheme 3. Construction of the CDE Ring System via an Intramolecular Nitrile Oxide Cycloaddition



With the olefins differentiated by the cycloaddition, our attention was next focused on a hydrogenation of the remaining olefin at C20. Prior to hydrogenation, the isoxazoline **25** was reduced with DIBALH in toluene at −20 °C to yield isoxazolidine **26** in 97% yield.[19] Although the olefin at C20 was unreactive due to steric hindrance, the hydrogenation of C20 olefin could be effected by the use of PtO_2 as a catalyst, whereby N−O bond cleavage also occurred to give amino alcohol **27**. The diastereomeric ratio of **27** was determined to be 4.3:1 by ^{1}H NMR analysis after protection of the amino group with $ClCO_2Me$ in the presence of Na_2CO_3 followed by Dess−Martin oxidation (67% yield, three steps from **26**).[20] While unprecedented in the literature, we found that exposure of ketone **29** to 5% TFA in toluene at 60 °C resulted in the elimination of the superfluous (methoxycarbonyl)amino group at the β position of the carbonyl group, leading to the formation of enone **4** in 86% yield.

The remaining operation necessary for synthesis of the CDE ring portion of scillascilloside E-1 involved a stereoselective introduction of an angular methyl group at C14. In this regard, Corey and co-workers reported in their synthesis of lanostenol that a cyclopropanation of the TMS enol ether, prepared from Grundemann ketone, followed by base-catalyzed cleavage of the resultant cyclopropyl carbinol resulted in the preferential formation of a *trans*-fused hydrindane derivative.[3] However, in our case, cyclopropanation of the TMS enol ether derived from enone **4** proceeded from the convex β face, leading to

Scheme 4. Completion of the Synthesis of the CDE Ring Fragment



predominant formation of the *cis*-fused isomer after treatment with NaOH.[21] Given these results, a decision was made to reduce the carbonyl group at C8 in preparation for the hydroxyl-directed cyclopropanation reaction.[22] As anticipated, Luche reduction[23] took place selectively from the less hindered β face to give allyl alcohol **30** (91% yield), which underwent cyclopropanation[24] to afford cyclopropyl alcohol **31** exclusively in 92% yield. While hydrogenolytic cleavage of the three-membered ring in **31** did not occur even at elevated temperature under high-pressure conditions, this problem was effectively circumvented by removal of the TBDPS group at C24 with Bu_4NF in THF (96% yield), leading to the exclusive formation of *trans*-fused hydrindane **33** in 74% yield.[25] Reprotection of the primary alcohol with TBDPSCl was followed by oxidation of the secondary alcohol with Dess−Martin periodinane to give ketone **3** in 84% yield in two steps, thereby completing the synthesis of the CDE ring system of scillascilloside E-1 (Scheme 4).

dx.doi.org/10.1021/ol500657f | *Org. Lett.* 2014, 16, 2054−2057

In summary, we have achieved a stereoselective synthesis of the [6,5,5]-tricyclic ring portion of scillascilloside E-1. This synthesis features simultaneous and stereoselective construction of the contiguous tetrasubstituted stereocenters (C13 and C17) by an Ireland−Claisen rearrangement and D ring formation by an intramolecular nitrile oxide cycloaddition. Further efforts toward a total synthesis of scillascilloside E-1 are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nakamura@phar.nagoya-cu.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported in part by the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research), the Ministry of Education, Culture, Sports, Science and Technology, Japan (Platform for Drug Discovery, Informatics, and Structural Life Science), the Uehara Memorial Foundation, and the Naito Foundation. We are grateful to the Fukuyama group of Nagoya University for the use of their mass spectrometer.

■ REFERENCES

(1) Sholichin, M.; Miyahara, K.; Kawasaki, T. *Chem. Pharm. Bull.* **1985**, *33*, 1756−1759.
(2) Lee, S.-M.; Chun, H.-K.; Lee, C.-H.; Min, B.-S.; Lee, E.-S.; Kho, Y.-H. *Chem. Pharm. Bull.* **2002**, *50*, 1245−1249.
(3) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149−9152.
(4) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 6764−6768.
(5) Akahori, Y.; Yamakoshi, H.; Sawayama, Y.; Hashimoto, S.; Nakamura, S. *J. Org. Chem.* **2014**, *79*, 720−735.
(6) ter Halle, R.; Bernet, Y.; Billard, S.; Bufferne, C.; Carlier, P.; Delaitre, C.; Flouzat, C.; Humblot, G.; Laigle, J. C.; Lombard, F.; Wilmouth, S. *Org. Process Res. Dev.* **2004**, *8*, 283−286.
(7) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997−3000.
(8) (a) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084−8090. (b) Schöllkopf, U.; Bánhidai, B.; Frasnelli, H.; Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767−1783.
(9) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022.
(10) (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223−5230. (b) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417−1423. (c) Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721−731. (d) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A. *Tetrahedron* **1993**, *49*, 5109−5126.
(11) (a) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887−2890. (b) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320−328. (c) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047−3050.
(12) For reviews on Ireland−Claisen rearrangements, see: (a) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905−2928. (b) McFarland, C. M.; McIntosh, M. C. The Ireland−Claisen Rearrangement (1972−2004). In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; pp 117−210. (c) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133−3148.
(13) For a precedent for simultaneous construction of contiguous tetrasubstituted stereocenters by an Ireland−Claisen rearrangement of cyclohex-2-enyl esters, see: Gu, Z.; Herrmann, A. T.; Stivala, C. E.; Zakarian, A. *Synlett* **2010**, 1717−1722.
(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(15) For a review on Henry reaction, see: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945.
(16) For recent reviews on 1,3-dipolar cycloadditions, see: (a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247−12275. (b) Rane, D.; Sibi, M. *Curr. Org. Synth.* **2011**, *8*, 616−627. (c) Browder, C. C. *Curr. Org. Synth.* **2011**, *8*, 628−644.
(17) For combinational use of Ireland−Claisen rearrangement and intramolecular nitrile oxide cycloaddition for the synthesis of bicyclic compounds, see: (a) Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev, V. S. *Chem.—Eur. J.* **2006**, *12*, 5992−6001. (b) Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930−5939. (c) Parthasarathy, G.; Besnard, C.; Kündig, E. P. *Chem. Commun.* **2012**, *48*, 11241−11243.
(18) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5342.
(19) For a review on cleavage of isoxazolines, see: Nagireddy, J. R.; Raheem, M.-A.; Haner, J.; Tam, W. *Curr. Org. Synth.* **2011**, *8*, 659−700.
(20) The stereochemistry at C20 of major isomer **29** was confirmed by a crosspeak between C20-CH_3 and C23-H in the NOESY spectrum of enone **4**.
(21) A similar observation was made by Kobayashi and co-workers during their synthesis of fomitellic acid B. See ref 4.
(22) For a review on heteroatom-directed organic reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(23) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(24) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353−3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58.
(25) The stereochemistry at C14 was unambiguously confirmed by a crosspeak between C14-CH_3 and C9-H_{ax} in the NOESY spectrum of ketone **3**.