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Enantioselective Syntheses of (+)-Xylarenal A and *ent*-Xylarenal A

Sandra Díaz, Asensio González, Ben Bradshaw, Javier Cuesta, and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain

josep.bonjoch@ub.edu

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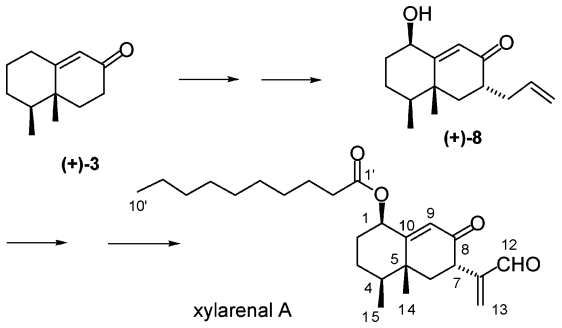

The total synthesis of the sesquiterpenoid xylarenal A is reported. This first synthetic entry to an eremophilane terpenoid with an exocyclic vinyl aldehyde unit involves the use of the bicyclic enone (+)-**3**, which after a γ-oxidation and α'-allylation leads to the formation of the ketone (+)-**8**. After its acylation, an oxidative cleavage of the allyl side chain followed by α-methylenation of the resulting aldehyde gives (+)-xylarenal A (**1**). The synthesis of (−)-xylarenal A from (−)-**3** is also reported. Moreover, the first total synthesis of the trinoreremophilane (+)-1α-hydroxyisoondetianone (**5**) is described.

The rare eremophilane sesquiterpenoids[1] embodying the 8-oxo-9,11-eremophiladien-12-al motif[2] are biogenetically related natural products that have been recently isolated from *Xylaria* fungi (Figure 1). A total synthesis of these novel sesquiterpenoids, which show noteworthy pharmacological activities such as an HIV-1 integrase inhibition (integric acid),[3] NPY-receptor antagonism (xylarenals A and B),[4] and cytotoxicity toward a CCRFCEM leukemia line (eremophilane 07H239-A),[5,6] has yet to be reported.

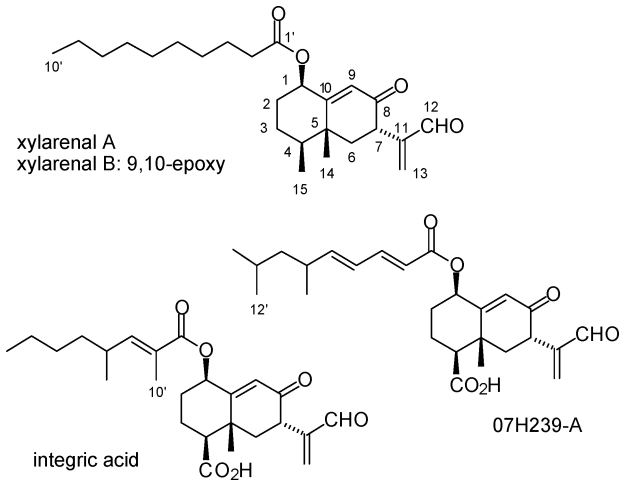

FIGURE 1. Structure of xylarenals and related sesquiterpenoids.

Xylarenal A (**1**) was isolated from the fermentation broth of a fungal strain, *Xylaria persicaria*, by a team of Merck scientists,[4] the fungus being retrieved from fallen fruits of *Liquidambar styraciflua* L. collected in eastern North America.[7] The structure of **1** was determined using NMR spectroscopy, and the absolute configuration was not assigned. It was demonstrated that xylarenals are selective ligands for the NPY Y5 receptor, which according to genetic and pharmacological studies is involved in mediating food intake and body weight.[8,9]

In this paper, we describe the total synthesis of (+)-xylarenal A (**1**), which constitutes the first synthetic entry to an eremophilane sesquiterpene embodying a vinyl aldehyde linked to the decalin ring skeleton and allows the absolute configuration of xylarenal A to be established. Additionally, the synthesis of 1α-hydroxyisoondetianone,[10] which is formed in the course of the synthetic route to xylarenal A, is reported. This trinoreremophilane was isolated by Bohlmann from aerial parts of *Ondetia linearis* in 1989.

Results and Discussion

Our synthetic planning (Figure 2) was based on the use of the enantiopure bicyclic enone **3**[11] as the advanced

(1) For recent biosynthetic studies about eremophilane sesquiterpenes, see: (a) Calvert, M. J.; Ashton, P. R.; Allemann, R. K. *J. Am. Chem. Soc*. **2002**, *124*, 11636−11641. (b) Zhao, Y.; Schenk, D. J.; Takahashi, S.; Chappell, J.; Coates, R. M. *J. Org. Chem.* **2004**, *69*, 7428−7435. (c) Felicetti, B.; Cane, D. E. *J. Am. Chem. Soc*. **2004**, *126*, 7212−7221.

(2) Numbering according to: Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1992.

(3) (a) Singh, S. B.; Zink, D.; Polishook, J.; Valentino, D.; Shafiee, A.; Silverman, K.; Felock, P.; Teran, A.; Vilella, D.; Hazuda, D. J.; Lingham, R. B. *Tetrahedron Lett.* **1999**, *40*, 8775−8779. (b) Singh, S. B.; Felock, P.; Hazuda, D. J. *Biorg. Med. Chem. Lett.* **2000**, *10*, 235−238.

(4) Smith, C. J.; Morin, N. R.; Bills, G. F.; Dombrowski, A. W.; Salituro, G. M.; Smith, S. K.; Zhao, A.; MacNeil, D. J. *J. Org. Chem.* **2002**, *67*, 5001−5004

(5) McDonald, L. A.; Barbieri, L. R.; Bernan, V. S.; Janso, J.; Lassota, P.; Carter, G. T. *J. Nat. Prod.* **2004**, *67*, 1565−1567.

(6) For other eremophilane sesquiterpenes with the same vinylaldehyde unit (C11−C13) linked to the decalin ring, see: (a) 9-Oxoeremophila-10,11(13)-dien-12-al: Abell, A. D.; Massy-Westropp, R. A. *Aust. J. Chem.* **1985**, *38*, 1263−1269. (b) Bipolaroxin: Sugawara, F.; Strobel, G.; Fisher, L. E.; Van Duyne, G. D.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8291−8294. (c) Bipolal: Watanabe, N.; Fujita, A.; Ban, N.; Yagi, A.; Etoh, H.; Ina, K.; Sakata, K. *J. Nat. Prod*. **1995**, *58*, 463−466. (d) KM-01: Kim, S.; Hatori, M.; Ojika, M.; Sakagami, Y.; Marumo, S. *Bioorg. Med. Chem*. **1998**, *6*, 1975−1982. (e) Sch420789: Puar, M. S.; Barrabee, E.; Hallade, M.; Patel, M. *J. Antibiot.* **2000**, *53*, 837−838.

(7) Rogers, J. D. *Can. J. Bot.* **1979**, *57*, 941−945.

(8) Gehlert, D. R. *Neuropeptides* **1999**, *33*, 329−338.

(9) For recent studies about the neuropeptide Y, see: Blum, C.; Zheng, X.; de Lombaert, S. *J. Med. Chem.* **2004**, *47*, 2318−2325.

(10) Zdero, C.; Bohlmann, F. *Phytochemistry* **1989**, *28*, 1653−1660. Terpene nomenclature, 1α-hydroxy-11,12,13-trinor-9-eremophilen-8-one; systematic name, (4a*R*,5*S*,8*S*)-8-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one.

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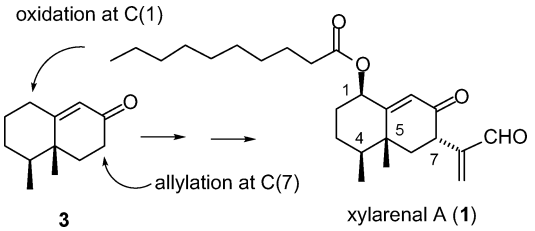
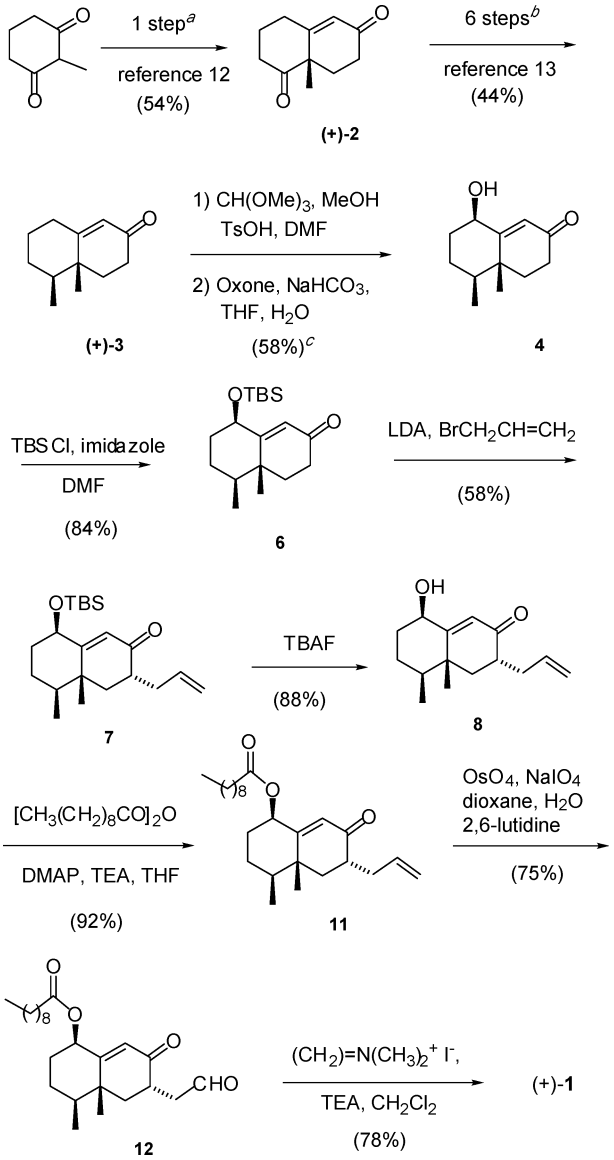


FIGURE 2. Proposed synthetic pathway to xylarenal A.

synthetic intermediate, which as well as ensuring a known configuration for the two stereogenic centers at C(4) and C(5)[2] might also allow good stereocontrol in the genesis of the stereogenic centers at C(1) and C(7). As starting material for the synthesis of target **1**, shown in Scheme 1, we used the (+)-Wieland−Miescher ketone **2**,[12] which is available from 2-methyl-1,3-cyclohexanedione by an asymmetric process promoted by L-proline. Following the protocol developed by Paquette[13] allowed the building block **2**, which has been widely used in the synthesis of terpenoids and steroids, to be transformed in a six-step sequence into the bicyclic enone (+)-**3**,[14] which is the common intermediate for the syntheses reported here (Scheme 1).

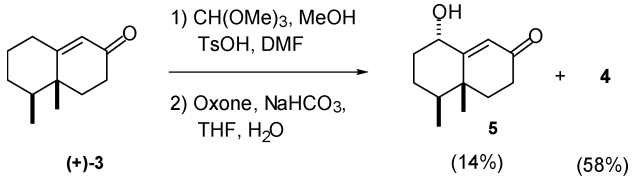
As the crucial steps in our approach to **1**, we planned an oxidation at C(1) to be followed by the formation of the C(7)−C(11) bond, incorporating a latent acetaldehyde side chain. Oxidation of **3** to install the hydroxyl group at C(1) was carried out through its dienol ether (not shown), which was treated by oxone under the conditions reported by Fuchs in the steroid field.[15,16] The stereochemical outcome of this oxidation (Scheme 2), which furnished the axial alcohol **4** (58%) and its equatorial epimer **5** (14%),[17] is consistent with that observed in closely related systems.[18] The configuration of alcohols **4** and **5** was assigned on the basis of the coupling pattern/chemical shift observed for methine protons at C(1) and C(9): axial alcohol **4** displays signals at δ 4.31 (t, $J = 3$ Hz) and 5.81, respectively, while the equatorial alcohol shows the two signals at δ 4.30 (ddd, $J = 11.5$, 5.6, 1.9 Hz) and 6.19. Compared to its epimer, the latter is deshielded due to the anisotropic effect of the near hydroxyl group.

SCHEME 1. Synthesis of Xylarenal A



[a] Methyl vinyl ketone, L-proline. [b](i) $(CH_2SH)_2$, TsOH; (ii) $Ph_3P{=}CHOCH_3$, then HCl; (iii) $NaBH_4$; (iv) MsCl; (v) $LiBHEt_3$; (vi) $Tl(NO_3)_3$. [c]See Scheme 2.

SCHEME 2. Synthesis of (+)-1-Hydroxyisoondetianone (5)



Both epimers (**4** and **5**) were interconverted through a Mitsunobu process: i) p-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD; ii) $LiOH{\cdot}H_2O$, MeOH.

(**4** → **5**) 69% ⟹ (54% overall yield of (+) -**5** from (+) -**3**)

(**5** → **4**) 67% ⟹ (68% overall yield of (+) -**4** from (+) -**3**)

Interestingly, the minor alcohol formed corresponds to the trinorsesquiterpenoid 1α-hydroxyisoondetianone (**5**),[10] whose ^{1}H NMR and optical rotation data coincide fully

(11) (4a*R*,5*S*)-Enantiomer was initially selected as an enantiopure advanced precursor for biogenetic considerations, and later it was found to be an adequate choice to build up the correct stereochemistry for **1**.

(12) (a) Buchschacher, P.; Fürst, A. *Org. Synth.* **1985**, *63*, 37−43. (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53−56.

(13) Paquette, L. A.; Wang, T.-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367−3374

(14) For an alternative synthesis of (+)-**3** from carvone, see: Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073−10082.

(15) Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902−921 and references therein.

(16) For the γ-oxidation of enones through their methyl dienol ether using *m*-CPBA, see: Kirk, D. N.; Wiles, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1015−1016.

(17) Compounds **4** and **5** have been previously reported in the racemic series from *rac*-**3** via a rather lengthy route involving a six-step sequence: Hagiwara, H.; Uda, H,; Kodama, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 963−977.

(18) For the γ-hydroxylation of the 15-norderivative of *rac*-**3**, see: (a) Holland, H.; Auret, B. *Can. J. Chem.* **1975**, *53*, 2041−2044. (b) Wege, P. M.; Clark, R. D. Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144−3148. (c) Wijnberg, J.; Vader, J.; deGroot, A. *J. Org. Chem.* **1983**, *48*, 4380−4387. (d) Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 7215−7223.

with those of the natural product, allowing the absolute configuration of this terpenoid to be determined.[17] This natural product was obtained in a better yield by converting its epimer, alcohol **4**, into **5** through a Mitsunobu process,[19] followed by a saponification of the nitrophenylbenzoate initially formed.[20] Thus, the overall yield for the transformation of (+)-**3** into (+)-**5** is 54% (Scheme 2).

Returning to the synthetic sequence to xylarenal A, to optimize the yield of the required alcohol **4**, the minor epimer **5** was converted to axial alcohol **4** using the above Mitsunobu protocol with a 67% yield, thus increasing the overall yield of the transformation (**3** → **4**) to 68%. Alcohol **4** was then protected with TBSCl, to give compound **6** in 84% yield. Treatment of the kinetic enolate of **6**[21] with allyl bromide diastereoselectively gave compound **7** in 55% yield (74% based on recovered ketone **6**).[22] After removal of the TBS group from **7** using TBAF, alcohol **8** was isolated in 88% yield.[23] The configuration at C(7) was established by means of NOESY experiments, which showed a strong cross-peak connecting H-7_{ax} and the C(14) methyl group. Moreover, the chemical shift (δ 18.3) of C(14) is diagnostic of the equatorial disposition of the allyl group from compound **7** onward.

At this point, we decided to examine the sequence in reverse with an initial allylation at C(7) followed by an oxidation at C(1) to avoid the protection/deprotection steps.[24] When the allylation process was carried out from **3**, the conversion to ketone **10** was achieved in 52% yield, the diallylated derivative being isolated in 12% yield. However, the γ-oxidation now took place in only 34% yield to give alcohol **8** together with 10% of its epimer at C(1). So, although this sequence (**3** → **8**) only requires two steps, its overall yield (17%) compared with that obtained in the sequence depicted in Scheme 1 (29%) led us to discard this protocol.

We pursued the synthetic process by means of esterification of alcohol **8** with decanoic anhydride to achieve the characteristic side chain of the target at C(1),

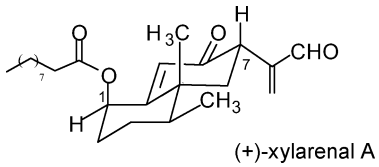


FIGURE 3. Stereofigure of (+)-xylarenal A.

compound **11** being isolated in nearly quantitative yield. The last phase of the xylarenal A synthesis implies the oxidation of the allyl moiety to achieve aldehyde **12**, which should be submitted to a methylenation process. While the ozonolysis cleavage of **11** was unsuccessful, the catalytic OsO_4 process, using 2,6-lutidine as an additive,[25] led satisfactorily to aldehyde **12**. Finally, the C(13) methylene was installed in only one step by a reaction of **12** with dimethyl methyleneammonium iodide (Eschenmoser's salt) in CH_2Cl_2 and triethylamine as a base,[26,27] which proceeded smoothly to give **1** in 78% yield.

Compound **1** had NMR spectral data matching those reported for the isolated xylarenal A,[28] which allowed us to conclude that the stereostructure of the natural product corresponds to that of **1**. The dextrorotatory power of **1**, $[\alpha]_D$ + 28.2 (*c* 0.45, CH_2Cl_2), has enabled the absolute configuration of the bicyclic core of xylarenal A to be established as 1*R*,4*S*,5*R*,7*S*.[29]

In summary, the first synthesis of (+)-xylarenal A has been accomplished (14 steps from (+)-Wieland−Miescher ketone, 7% overall yield). The route here described is the first to achieve sesquiterpenoids embodying an α,β-unsaturated aldehyde moiety directly attached to the α'-position of the bicyclic enone motif.[30,31]

Building on this approach, the synthetic entry to the nonnatural enantiomer is also possible since the key intermediate **3** is available in its levo form.[32] Thus, starting from (−)-**3**,[33] which is obtained in 28% yield from the commercially available (*R*)-3-methylcyclohexanone, and following the same protocol described in Scheme 1,

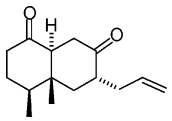
(19) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(20) For a related process, see: Lejeune, J.; Lallemand, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2977−2980.

(21) For α'-allylation of related bicyclic enones, see: (a) Zoretic, P. A.; Ferrari, J. L.; Bhakta, C.; Barcelos, F.; Branchaud, B. *J. Org. Chem.* **1982**, *47*, 7, 1327−1329. (b) Bell, R. P.; Wijnberg, J.; de Groot, A. *J. Org. Chem.* **2001**, *66*, 2350−2357.

(22) This yield was obtained working on a 0.4 mmol scale. Working on a 4 mmol scale affords a slightly better yield (58%), but compound **7** is formed together with the diallylated derivative (not shown) in 25% yield. These compounds are not easy to separate at this stage, but after the deprotection step their corresponding alcohols can be separated.

(23) Deprotection of **7** using acidic conditions leads to the formation of considerable amounts of the diketone **9**.



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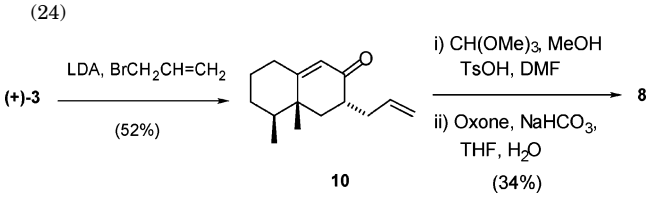
(24)



(25) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219

(26) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1989**, 1283−1284.

(27) For some examples of this direct α-methylenation of aldehydes in the natural product synthesis, see: (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558−3575. (b) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929−8936. (c) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508−511. (d) Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637−3640.

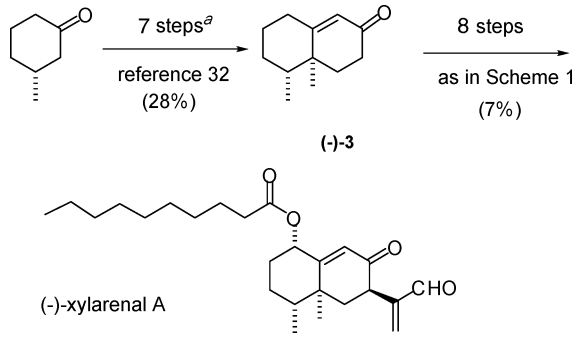
(28) Due to the dearth of the natural product (personal communication of Dr. Cameron J. Smith, Merck & Co., Inc.), we were unable to obtain a sample of natural xylarenal A. In the communication, it became clear that xylarenal A is unstable on storage, even when kept in the freezer.

(29) Xylarenal A: terpene name, 1-decyloxycarbonyl-8-oxo-9,11(13)-eremophiladien-12-al; systematic name, (3*S*,4a*R*,5*S*,8*R*)-8-decyloxycarbonyl-3-[(1-formyl)vinyl]-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one.

(30) This structural motif is also found in the monoterpenoid vesperal, which has been synthesized but through synthetic procedures that are not easily applicable, if at all, to obtain **1**. *rac*-Vesperal: Boyer, F. D.; Malosse, C.; Zagatti, P.; Einhorn, J. *Bull. Soc. Chim. Fr.* **1997**, 134, 757−764. (+)-Vesperal: Domon, K.; Mori, K. Eur. *J. Org. Chem.* **2000**, 3787−3785. Fuganti, C.; Serra, S. *Helv. Chim. Acta* **2002**, *85*, 2489−2502.

(31) For the elaboration of a vinyl aldehyde side chain in the eudesmane-type sesquiterpenes, see: Xiong, Z.; Yang, J.; Li, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 2607−2612.

SCHEME 3. Synthesis of (−)-Xylarenal A



[a] (i) HCO_2Et, NaOMe; (ii) PhNHMe; (iii) LDA, MeI; (iv) $Br(CH_2)_2CO_2Et$, K*t*-BuO; (v) 1 N HCl, THF, then 1 N NaOH; (vi) NaOAc, Ac_2O; (vii) $(MeO)_2POMe$, BuLi.

we have arrived at (−)-xylarenal A, $[\alpha]_D$ −32.7 (*c* 0.85, CH_2Cl_2) (Scheme 3).

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for compounds **1** and **4**−**12**, as well as ^1H and ^{13}C NMR copies for all reported compounds, including COSY and HSQC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0502450

(32) Cuesta, X.; González, A.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3365−3370. For another synthesis of (−)-**3**, see: Schenato, R. A.; dos Santos, E. M.; Tenius, B. S. M.; Costa, P. R. R.; Caracelli, I.; Zukerman-Schpector, J. *Tetrahedron: Asymmetry* **2001**, *12*, 579−584.

(33) We have prepared (−)-**3** by our procedure (ref 32) with some improvements: Díaz, S.; Cuesta, J.; González, A.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400−7406. The overall yield (28%) is the same as that obtained with Paquette's procedure (ref 13) using the (−)-Wieland−Miescher ketone.