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Asymmetric total syntheses of xanthatin and 11,13-dihydroxanthatin using a stereocontrolled conjugate allylation to γ-butenolide

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ABSTRACT

The stereocontrolled conjugate allylation to an optically pure γ-butenolide provided direct and reliable access to a *trans*-fused series of xanthanolide sesquiterpenoids and allowed for the enantioselective total syntheses of xanthatin and 11,13-dihydroxanthatin to be efficiently achieved.

1. Introduction

Xanthanolide sesquiterpenoids are primarily isolated from the plants of the genus *Xanthium* (family Compositae), with more than 100 compounds having been reported so far.[1] These compounds exhibit impressive biological properties, including allelopathic, antitumor, antimicrobial, anti-MRSA, anti-ulcerogenic, and anti-inflammatory activities. With regard to their chemical structure, they consist of a seven-membered carbocycle containing a *cis*- or *trans*-fused γ-butyrolactone at their C8 position (Fig. 1). These compounds have attracted increasing and considerable levels of attention from synthetic organic chemists and biological scientists because of their unique structures and promising biological profiles. Since the first total synthesis of 11,13-dihydroxanthatin (**2**) reported by Morken in 2005,[2,3] several syntheses of xanthanolide sesquiterpenoids have been reported by Martin,[4] Shishido,[5] Takikawa,[6] Tang,[7] and our own group.[8] Recently, Aramaki et al. reported the potent cell growth inhibitory activity of xanthatin (**1**) against the highly aggressive human breast cancer cell line MDA-MB-231, with the compound acting via a unique mechanism; selectively inducing the expression of the GADD45γ gene isoform.[9] With this in mind, the development of an efficient synthetic method for the construction of these compounds together with an understanding of their structure–activity relationship would be invaluable for investigating their mechanism of action and clinical potential.

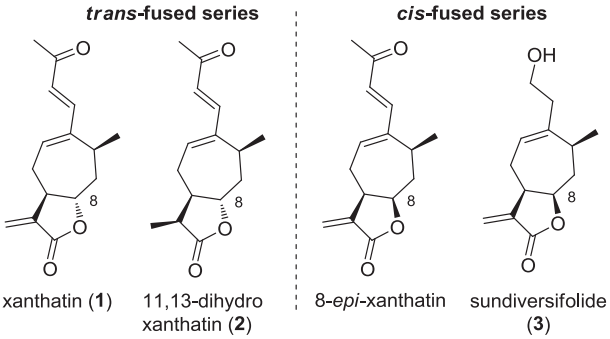

Fig. 1. Naturally occurring xanthanolides.

During the course of our studies toward the development of a systematic synthetic approach to xanthanolides,[8] we recently reported our initial syntheses of the *trans*-fused xanthanolides, xanthatin (**1**) and 11,13-dihydroxanthatin (**2**), that involved an intramolecular acylation and one-pot Wittig lactonization. Unfortunately, however, this method was not amenable to large scale preparation because it involved too many steps (28 steps in the linear sequence). In our previous work, the *cis*-fused γ-butyrolactone **4** was used as a common chiral building block, as it was the synthetic intermediate in our previous synthesis of

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sundiversifolide (**3**),[8a,c] and thus several tedious steps were required to transform the *cis*-fused bicyclic lactone **4** into the *trans*-fused lactone **5** (Fig. 2). The development of an alternative route for the direct stereocontrolled construction of the *trans*-fused xanthanolide core skeleton therefore represents a significant challenge. In the current work, we have described the efficient and step-economical second-generation asymmetric syntheses of xanthatin (**1**) and 11,13-dihydroxanthatin (**2**), based on the highly stereoselective conjugate allylation of the γ-butenolide.

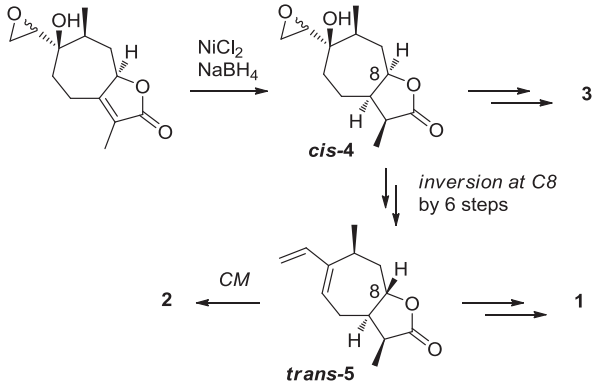
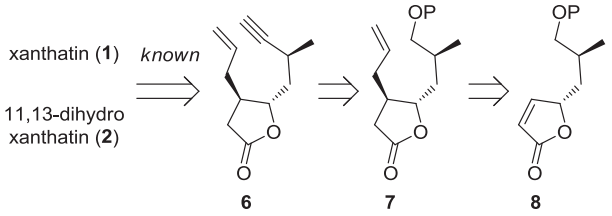


Fig. 2. Our previous studies on the syntheses of xanthanolides.

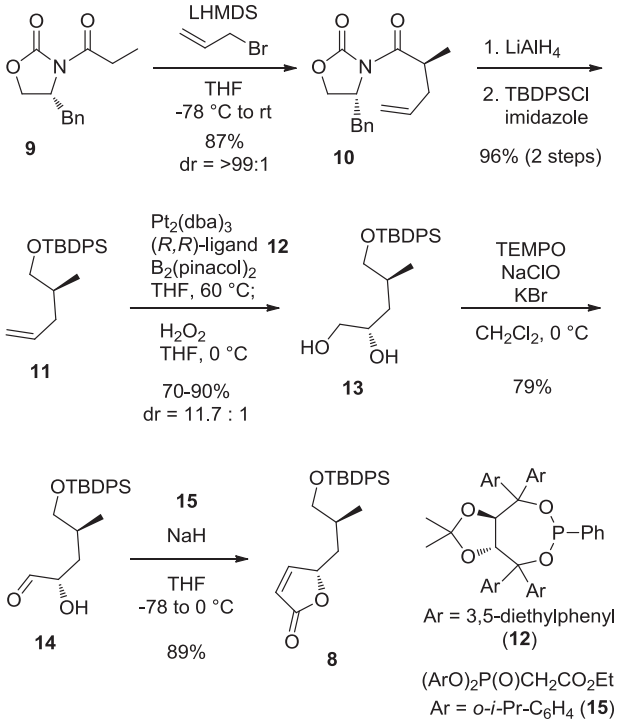
2. Results and discussion

Our retrosynthetic analysis is shown in Scheme 1. The key point of our synthetic strategy was the development of a direct and general synthetic route for the stereoselective construction of a series of *trans*-fused xanthanolides. With this in mind, enyne **6** was targeted as the required intermediate because the seven-membered ring with the (*E*)-conjugated dienone moiety could be efficiently constructed by the enyne ring closing metathesis (RCM) and cross metathesis processes according to the approach reported by Morken[3] and Martin.[4] The rapid and stereoselective assembly of the *trans*-3,4-disubstituted-γ-butyrolactone bearing an allyl substituent was particularly challenging. We anticipated that the stereoselective installation of the allyl moiety of enyne **6** could be achieved by the conjugate allylation of the optically active γ-butenolide **8**, because this conjugate reaction was expected to proceed from the opposite face of the side chain in **8**.



Scheme 1. Retrosynthetic strategy of xanthatin (**1**) and 11,13-dihydroxanthatin (**2**).

Our synthesis commenced with the asymmetric alkylation of the Evans oxazolidinone **9** with allyl bromide to give **10** in 87% with a high level of diastereoselectivity (Scheme 2).[10] The amide **10** was subjected to reduction with lithium aluminum hydride and the resulting alcohol was protected with TBDPSCl to give **11** in 96% yield over the two steps. We then examined the stereocontrolled construction of the chiral center at C8 (xanthatin numbering). Unfortunately, however, the application of the standard Sharpless asymmetric dihydroxylation conditions to the terminal alkene of **11** provided an unsatisfactory level of selectivity (almost 3:1). This lack of selectivity did not come as too much of a surprise, because the

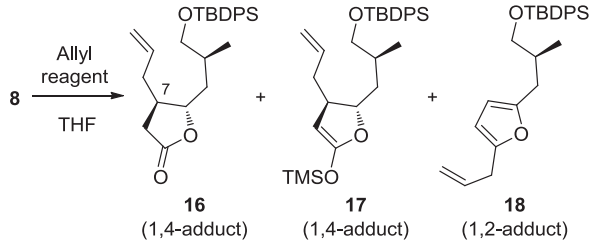


Scheme 2. Synthesis of the γ-butenolide (**8**).

enantioselective dihydroxylation of simple terminal alkenes has been reported as a challenging reaction.[11] Pleasingly, an enhanced level of selectivity was obtained using the Pt-catalyzed enantioselective diboration method developed by Morken et al.[12] According to this procedure, **3** was treated with bis(pinacolato)diboron in the presence of $Pt_2(dba)_3$ and the phosphonite ligand **12** at 60 °C followed by oxidative workup with H_2O_2 to give diol **13** in yields of 70–90% with a high level of diastereoselectivity. The diol **13** was then selectively oxidized with TEMPO[13] to provide the α-hydroxy aldehyde **14**, which was subjected to lactonization. Although our initial attempts at the lactonization of **14** using our own methods involving ynolate-initiated lactonization[14] or tandem acylation-Wittig lactonization[15] resulted in low yields, we found that the *Z* selective olefination of **14** with the phosphonic ester **15**[16] and subsequent lactonization proceeded smoothly to afford the γ-butenolide **8** in 89% yield.

With a significant quantity of the optically active γ-butenolide **8** in hand, our attention turned to the development of a stereocontrolled conjugate allylation that would provide direct access to the required *trans*-3,4-disubstituted-γ-butyrolactone bearing the allyl side chain. Conjugate allylation reactions to α,β-unsaturated carbonyl compounds are fundamentally important methods in organic synthesis, and catalytic and enantioselective versions of these processes have been extensively studied.[17,18] Unfortunately however, to the best of our knowledge, the majority of these reactions are limited to α,β-unsaturated ketones, esters, and amides, and the conjugate allylation of lactones, with particularly emphasis on five-membered α,β-unsaturated lactones, has been scarcely reported.[19] With this in mind, we therefore examined the conjugate allylation of the γ-butenolide **8** to identify an efficient protocol for the synthesis of *trans*-3,4-disubstituted-γ-butyrolactone (Table 1). Our initial attempts using allylsilane were unsuccessful, and in the case of allylstannane, only the unreacted starting material was found in the reaction mixture (entries 1 and 2). The copper catalyzed addition of allylmagnesium chloride resulted only in the formation of the undesired product **18**, which was formed from the 1,2-addition of the allyl reagent followed by

Table 1
Conjugate allylation of the optically active γ-butenolide **8**

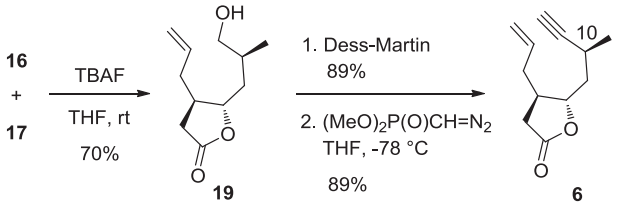


Entry	Allyl reagent	Temp (°C)	Yield (%) **16**+**17**	**16**/**17**
1	$AllylSiMe_3$, Tf_2NH	−78 to 0	Messy	—
2	$AllylSnBu_3$, $TiCl_4$	−78 to rt	0	—
3	AllylMgCl, CuI (cat.)	−78	0[a]	—
4	$(Allyl)_2CuLi$	−100 to 0	0	—
5	$(Allyl)_2Cu(CN)Li_2$	−78 to 0	21	21:0
6	(Allyl)Cu·MgCl·I, TMSCl	−78 to −40	64	39:25

[a] The 1,2-adduct **18** was obtained in 53% yield.

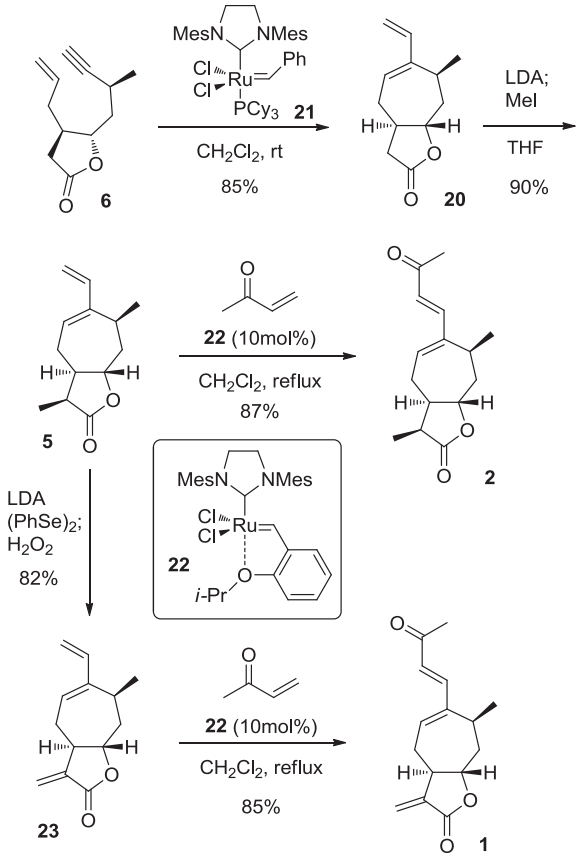
dehydration (entry 3). Pleasingly, when lithium diallylcuprate and lithium diallylcyanocuprate were employed in the conjugate addition, the 1,4-adduct **16** was isolated in moderate yield (entry 5). Encouraged by this result, we screened the reaction extensively using of $CuBr_2 \cdot SMe_2$, lithium salts, and several other Lewis acids. Following the screening process, the use of an allylcopper reagent in the presence of TMSCl, as reported by Lipshutz,[20] was found to work most efficiently for this transformation (entry 6). Under these conditions, the *trans*-1,4-adducts **16** and the corresponding TMS enol ether **17** were isolated in a combined yield of 64%. Pleasingly, the cis isomer was not detected in the crude products by ^1H NMR spectroscopy.

This mixture of **16** and **17** was then treated with TBAF to give alcohol **19** in 70% yield (Scheme 3). The alcohol **19** was then oxidized with Dess–Martin periodinane, and the resulting aldehyde was treated with Gilberts reagent[21] at −78 °C to provide enyne **6** in good overall yield without any epimerization at the C10 position.[22]



Scheme 3. Synthesis of the enyne **6**.

With the key compound **6** in hand, we proceeded to complete the total syntheses of the xanthanolides (Scheme 4). The ring closing metathesis of the enyne **6** was performed using the Grubbs catalyst **21** to give the seven-membered carbocycle **20** in 85% yield. Methylation of the lactone moiety of **20** proceeded stereoselectively to provide **5**, which was subjected to cross metathesis with methyl vinyl ketone using the Hoveyda catalyst **22**[23] to yield 11,13-dihydroxanthatin (**2**) in 87% yield, with the entire linear sequence totaling 13 steps. For the synthesis of xanthatin, the γ-butyrolactone **5** was treated with LDA and diphenyl diselenide to give the α-selenylated γ-butyrolactone, which was treated in situ with H_2O_2 to give the *exo*-methylene lactone **23** in 82% yield for the one-pot procedure. Finally, the cross metathesis of **23** under the conditions described above gave xanthatin (**1**) in 85% yield. All the spectra and the optical rotations of the synthetic materials **1** and **2** were identical to those of the natural products.



Scheme 4. Syntheses of xanthatin and 11,13-dihydroxanthatin.

3. Conclusion

In conclusion, we have achieved the development of a direct and highly efficient synthetic strategy for the construction of *trans*-fused xanthanolides using a stereocontrolled conjugate allylation to a γ-butenolide, allowing for the synthesis of xanthatin and 11,13-dihydroxanthatin in only 14 and 13 steps, respectively, and providing a level of efficiency much greater than that achieved by any of the previously reported synthetic approaches. Our synthetic route provides a powerful and general approach to the xanthanolides and other natural products possessing the *trans*-fused γ-butyrolactone.[24]

4. Experimental

4.1. General procedures

^1H NMR, ^{13}C NMR were measured in $CDCl_3$ solution using JEOL JNM-AL-400 spectrometer (^1H NMR at 400 MHz, ^{13}C NMR at 100 MHz) or a JNM-ECA-600 spectrometer (^1H NMR at 600 MHz, ^{13}C NMR at 150 MHz) using the reference standard (^1H NMR at 0.00 ppm (TMS), ^{13}C NMR at 77.0 ppm ($CDCl_3$)). Chemical sifts are reported in parts per million. Peak multiplicities are used the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet; br, broadened. IR spectra were recorded on JAS.CO FT/IR-410 or Shimadzu FT/IR-8300 spectrometers. Mass spectra and high-resolution mass spectra were obtained on JMS-K9, JEOL JMS-700 or Shimadzu LCMS-2010EV mass spectrometers. Elemental analyses were performed with YANACO 026 CHN analyzer. Melting points were measured with a Yanaco MP-500D apparatus or Büchi 535 melting point apparatus

and are uncorrected. Thin-layer chromatography (TLC) was performed on pre-coated plates (0.25 mm, silica gel Merck 60F_{245}). Column chromatography was performed on silica gel (Kanto Chemical Co., Inc.). Preparative HPLC was performed on a system utilizing a HITACHI L-6250 Intelligent Pump with a gradient solvent system of hexane and ethyl acetate and UV detector L-7400 at 254 nm, and also a system utilizing a JAS.CO PU-2087 Intelligent Pump with Dynamic Mixer MX-2080-32 and UV detector UV-2075 and RI detector RI-2031. The recycling preparative HPLC was performed with LC-908, which was consisted of UV detector UV-310B and RI detector RI-5. All reactions were performed under an air atmosphere unless otherwise noted, and dry dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc., and other solvents were distilled. Unless otherwise noted, reagents were obtained from chemical sources and without further purification.

4.2. (4*R*)-4-Benzyl-3-[(2*S*)-2-methyl-4-pentenoyl]-1,3-oxazolidin-2-one[25] 10

To a solution of HMDS (50 mL, 217 mmol) in THF (500 mL), cooled to 0 °C under N_2, was added dropwise *n*-BuLi (90 mL, 217 mmol, 2.4 M in hexane). The reaction mixture was stirred at 0 °C for 30 min, cooled to −78 °C, and then the oxazolidinone[26] **9** (39 g, 167 mmol) was added dropwise. After being stirred for 2 h, allyl bromide (40 mL, 501 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 2 h, warmed to room temperature, and stirred for 2 h. The mixture was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with AcOEt, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and, concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (30% AcOEt/Hex) to afford 40 g (87%) of **10** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.19 (d, *J*=6.8 Hz, 3H), 2.21–2.27 (m, 1H), 2.50–2.56 (m, 1H), 2.70 (dd, *J*=13.1, 9.7 Hz, 1H), 3.29 (dd, *J*=13.1, 3.4 Hz, 1H), 3.87 (tq, *J*=6.9, 6.8 Hz, 1H), 4.16 (dd, *J*=8.9, 3.4 Hz, 1H), 4.18 (dd, *J*=8.9, 8.9 Hz, 1H), 4.67–4.71 (m, 1H), 5.07 (dd, *J*=8.9, 2.0 Hz, 1H), 5.11 (dd, *J*=17.2, 2.0 Hz, 1H), 5.83 (ddt, *J*=17.2, 9.7, 7.6 Hz, 1H), 7.22 (d, *J*=6.9 Hz, 2H), 7.28 (t, *J*=6.9 Hz, 1H), 7.33 (t, *J*=6.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.4 (q), 37.2 (d), 38.0 (t), 38.1 (t), 55.4 (d), 66.0 (t), 117.2 (t), 127.3 (d), 129.0 (d), 129.4 (d), 129.5 (d), 135.3 (d), 135.4 (s), 153.1 (s), 176.5 (s).

4.3. (4*S*)-5-*tert*-Butyldiphenylsiloxy-4-methyl-1-pentene 11

To a suspension of $LiAlH_4$ (3.6 g, 94 mmol) in Et_2O (400 mL), cooled to 0 °C under N_2, was added a solution of **10** (13 g, 47 mmol) in Et_2O (70 mL). The reaction mixture was stirred at 0 °C for 1 h and quenched by the careful addition of H_2O (14 mL). The resulting mixture was warmed to room temperature and stirred for 30 min. NaOH solution (1 M) and H_2O (14 mL) were successively added and the resulting mixture was stirred at room temperature for 30 min, filtered through a pad of Celite, carefully concentrated by rotary evaporator to afford a crude product, which was used without further purification. The obtained crude alcohol (19 g) was dissolved in CH_2Cl_2 (230 mL) and cooled to 0 °C. Imidazole (4.4 g, 65 mmol) and TBDPSCl (14 mL, 56 mmol) were added. The mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was quenched with H_2O, extracted with AcOEt, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (3% AcOEt/Hex) to afford 15.3 g (96% in two steps) of **11** as a colorless oil. $[\alpha]_D^{21}$ −2.4 (*c* 2.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.91 (d, *J*=6.2 Hz, 3H), 1.05 (s, 9H), 1.72–1.78 (m, 1H), 1.87–1.94 (m, 1H), 2.22–2.29 (m, 1H), 3.48 (dd, *J*=9.6, 6.2 Hz, 1H), 3.50 (dd, *J*=9.6, 6.2 Hz, 1H), 4.97 (dd, *J*=10.3, 1.4 Hz, 1H), 5.00 (dd, *J*=16.5, 1.4 Hz, 1H), 5.75 (ddt, *J*=16.5, 10.3, 7.6 Hz, 1H), 7.38 (t, *J*=7.6 Hz, 4H), 7.42 (t, *J*=7.6 Hz, 2H), 7.67 (dd, *J*=7.6, 1.4 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.4 (q), 19.3 (s), 26.6 (q), 35.7 (d), 37.6 (t), 68.3 (t), 115.7 (t), 127.6 (d), 129.5 (d), 134.0 (s), 135.6 (d), 137.3 (d). IR (neat): 3072, 2958, 2931, 2858, 1471, 1427, 1112 cm^{-1}. MS (FAB) *m*/*z* 337 (M^+−H), 281 (M^+−*t*-Bu), 199 (100%). HRMS (FAB) calcd for $C_{22}H_{29}OSi$ (M^+−H): 337.1988, found: 337.1985.

4.4. (2*S*,4*S*)-5-*tert*-Butyldiphenylsiloxy-4-methyl-1,2-pentandiol 13

To an oven-dried reaction vial with magnetic stir bar in the glove box were added $Pt_2(dba)_3$ (108 mg, 0.10 mmol), (*R*,*R*)-3,5-diethylphenyl-TADDOLPPh[12] (**12**) (190 mg, 0.12 mmol), $B_2(pin)_2$ (580 mg, 2.2 mmol), and THF (16 mL). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C for 30 min. A solution of **11** (670 mg, 2.0 mmol) in THF (4 mL) was added and the reaction mixture was stirred at 60 °C for 12 h. NaOH (3 M, 6 mL) and 30% hydrogen peroxide (3 mL) were added at 0 °C. The mixture was warmed to room temperature, stirred for 4 h, treated with saturated aqueous $Na_2S_2O_4$ at 0 °C, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (50% AcOEt/Hex) to afford 670 mg (90%) of **13** as a colorless oil. $[\alpha]_D^{21}$ −2.5 (*c* 0.28, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.86 (d, *J*=6.9 Hz, 3H), 1.06 (s, 9H), 1.37 (ddd, *J*=14.4, 6.9, 3.4 Hz, 1H), 1.90 (ddd, *J*=14.4, 10.3, 6.8 Hz, 1H), 1.85–1.93 (m, 1H), 2.02 (br, 1H), 3.38 (br, 1H), 3.42–3.47 (m, 1H), 3.49 (dd, *J*=10.3, 7.6 Hz, 1H), 3.56 (dd, *J*=10.3, 4.8 Hz, 1H), 3.59–3.64 (m, 1H), 3.80–3.84 (m, 1H), 7.38–7.45 (m, 6H), 7.66–7.68 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.6 (q), 19.2 (s), 26.8 (q), 33.7 (d), 38.8 (t), 67.4 (t), 70.0 (t), 70.8 (d), 127.7 (d), 129.8 (d), 133.2 (t), 135.6 (d). IR (neat): 3383, 2930, 2857, 1471, 1427, 1111 cm^{-1}. MS (FAB) *m*/*z* 373 (M^++H), 199 (100%). HRMS (FAB) calcd for $C_{22}H_{33}O_3Si$ (M^++H): 373.2199, found: 373.2201.

4.5. (2*S*,4*S*)-5-*tert*-Butyldiphenylsiloxy-2-hydroxy-4-methylpentanal 14

To a solution of **13** (4.5 g, 12.1 mmol) in CH_2Cl_2 (60 mL), cooled to 0 °C under N_2, were added saturated aqueous $NaHCO_3$ (60 mL), TEMPO (95 mg, 0.61 mmol), and KBr (1.5 g, 13.2 mmol). The mixture was stirred at 0 °C for 10 min and then 5% NaClO aqueous (19 mL, 13.2 mmol) was added. After being stirred for 20 min, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (20% AcOEt/Hex) to afford 3.5 g (79%) of **14** as a colorless oil. The aldehyde **14**, containing unidentified side-products, was used in the next step without its purification.

4.6. (5*S*)-5-[(2*S*)-3-*tert*-Butyldiphenylsiloxy-2-methylpropyl]furan-2(5*H*)-one 8

To a solution of ethyl [bis(*o*-isopropylphenyl)phosphono]acetate[27] (5.1 g, 13.0 mmol) in THF (90 mL) was added 60% NaH (480 mg, 11.9 mmol) under N_2. The reaction mixture was stirred at room temperature for 30 min, then cooled to −78 °C. A solution of **14** (4.0 g, 10.8 mmol) in THF (10 mL) was added to the mixture, which was stirred at room temperature for 3 h and then Et_2O and H_2O (25 mL) were added. The resultant mixture was extracted with Et_2O, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography

(20% AcOEt/Hex) to afford 3.8 g (89%) of **8** as a colorless oil. $[\alpha]_D^{21}$ +42.6 (*c* 0.65, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ: 1.00 (d, *J*=6.8 Hz, 3H), 1.05 (s, 9H), 1.59 (ddd, *J*=14.5, 8.9, 5.5 Hz, 1H), 1.79 (ddd, *J*=14.5, 8.9, 5.5 Hz, 1H), 1.94–2.03 (m, 1H), 3.50 (dd, *J*=10.2, 6.0 Hz, 1H), 3.54 (dd, *J*=10.2, 4.8 Hz, 1H), 5.12–5.18 (m, 1H), 6.08 (dd, *J*=5.5, 2.1 Hz, 1H), 7.38–7.45 (m, 7H), 7.64 (d, *J*=6.9 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.6 (q), 19.3 (s), 26.9 (q), 32.6 (d), 37.3 (t), 68.7 (t), 81.8 (d), 121.3 (d), 127.7 (d), 129.7 (d), 133.5 (s), 135.5 (d), 156.8 (d), 173.1 (s). IR (neat): 2958, 2931, 1759, 1427, 1111 cm^{-1}. MS (FAB) *m*/*z* 393 (M^+–H), 337 (M^+–*t*-Bu), 317 (M^+–C_6H_5, 100%). HRMS (FAB) calcd for $C_{24}H_{29}O_3Si$ (M^+–H): 393.1886, found: 393.1892.

4.7. (4*R*,5*S*)-4-Allyl-5-[(2*S*)-3-*tert*-butyldiphenylsiloxy-2-methylpropyl]dihydrofuran-2(3*H*)-one 16

To a solution of CuI (118 mg, 0.62 mmol) and dry LiBr (54 mg, 0.62 mmol) in THF (1 mL), cooled to −78 °C under N_2, were added dropwise allylmagnesium chloride (0.30 mL, 0.60 mmol, 2 M in THF), TMSCl (0.076 mL, 0.60 mmol), and a solution of **8** (79 mg, 0.20 mmol) in THF (1 mL). The mixture was stirred at −78 °C for 1 h, warmed to −40 °C, and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with AcOEt, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (10% AcOEt/Hex) to afford 34 mg (39%) of **16** and 25 mg (25%) of **17** as a colorless oil.

4.7.1. Compound ***16***. $[\alpha]_D^{21}$ −29.6 (*c* 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ: 0.97 (d, *J*=6.2 Hz, 3H), 1.05 (s, 9H), 1.46 (ddd, *J*=14.5, 10.2, 3.0 Hz, 1H), 1.78 (ddd, *J*=14.5, 10.2, 4.2 Hz, 1H), 1.93–2.01 (m, 1H), 2.10–2.30 (m, 4H), 2.64 (dd, *J*=17.2, 7.6 Hz, 1H), 3.47–3.53 (m, 2H), 4.23 (ddd, *J*=10.2, 6.2, 3.0 Hz, 1H), 5.06–5.12 (m, 2H), 5.70 (ddt, *J*=17.2, 9.6, 6.8 Hz, 1H), 7.37–7.44 (m, 6H), 7.65 (dd, *J*=6.8, 1.4 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.0 (q), 19.3 (s), 26.8 (q), 32.4 (d), 34.5 (t), 36.9 (t), 38.3 (t), 40.9 (d), 68.8 (t), 83.0 (d), 117.8 (t), 127.6 (d), 129.6 (d), 133.7 (s), 134.4 (d), 135.6 (d), 176.3 (s). IR (neat): 2958, 2931, 2858, 1776, 1112 cm^{-1}. MS (FAB) *m*/*z*: 435 (M^+–H), 379 (M^+–*t*-Bu), 359 (M^+–C_6H_5), 199 (100%). HRMS (FAB) calcd for $C_{27}H_{35}O_3Si$ (M^+–H): 435.2355, found: 435.2355.

4.7.2. Compound ***17***. ^1H NMR (600 MHz, $CDCl_3$) δ: 0.17 (s, 9H), 0.94 (d, *J*=7.2 Hz, 3H), 1.05 (s, 9H), 1.38 (ddd, *J*=13.8, 10.8, 3.0 Hz, 1H), 1.80 (ddd, *J*=13.8, 9.6, 3.6 Hz, 1H), 1.96–2.07 (m, 2H), 2.17–2.27 (m, 2H), 1.96–2.07 (m, 2H), 2.17–2.27 (m, 2H), 3.45–3.53 (m, 3H), 4.21 (ddd, *J*=9.6, 6.0, 3.0 Hz, 1H), 5.03–5.12 (m, 2H), 5.63–5.71 (m, 1H), 7.35–7.43 (m, 6H), 7.63–7.66 (m, 4H).

4.8. (4*R*,5*S*)-4-Allyl-5-[(2*S*)-3-hydroxy-2-methylpropyl]dihydrofuran-2(3*H*)-one 19

To a solution of **16** (500 mg, 1.1 mmol) in THF (11 mL), cooled to 0 °C under N_2, was added tetrabutylammonium fluoride (2.2 mL, 2.2 mmol, 1 M in THF). The reaction mixture was stirred at 0 °C for 5 min, allowed to warm to room temperature, and stirred for 4 h. Saturated aqueous $NaHCO_3$ was added and the resulting mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (40% AcOEt/Hex) to afford 152 mg (70%) of **19** as a colorless oil. $[\alpha]_D^{21}$ −64.8 (*c* 0.11, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ: 0.99 (d, *J*=7.2 Hz, 3H), 1.51 (ddd, *J*=14.4, 8.0, 3.0 Hz, 1H), 1.78 (ddd, *J*=14.4, 10.2, 4.8 Hz, 1H), 1.89–1.97 (m, 1H), 2.13–2.35 (m, 4H), 2.67 (dd, *J*=17.4, 7.8 Hz, 1H), 3.50 (dd, *J*=10.8, 6.0 Hz, 1H), 3.55 (dd, *J*=10.8, 5.4 Hz, 1H), 4.26 (ddd, *J*=10.2, 7.2, 3.0 Hz, 1H), 5.09–5.14 (m, 2H), 5.68–5.77 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 16.2 (q), 33.1 (d), 34.5 (t), 36.8 (t), 38.6 (t), 41.1 (d), 68.0 (t), 83.3 (d), 117.9 (t), 134.4 (d), 176.2 (s). IR (neat): 3431, 3078, 2958, 2924, 2875, 1471, 1772, 1641 cm^{-1}. MS (FAB) *m*/*z* 199 (M^++H), 154 (100%). HRMS (FAB) calcd for $C_{11}H_{19}O_3$ (M^+ +H): 199.1334, found: 199.1341.

4.9. (4*R*,5*S*)-4-Allyl-5-[(2*S*)-3-oxo-2-methylpropyl]dihydrofuran-2(3*H*)-one

To a solution of **19** (80 mg, 0.40 mmol) in CH_2Cl_2 (4 mL), cooled to 0 °C under N_2, was added Dess–Martin periodinane[28] (340 mg, 0.80 mmol). The reaction mixture was stirred at 0 °C for 10 min, stirred at room temperature for 10 min, and then saturated aqueous $NaHCO_3$ was added. The resulting mixture was extracted with AcOEt and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (30% AcOEt/Hex) to afford 71 mg (89%) of the aldehyde as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.21 (d, *J*=6.8 Hz, 3H), 1.65 (ddd, *J*=14.4, 8.9, 2.8 Hz, 1H), 2.26 (ddd, *J*=14.4, 10.3, 4.8 Hz, 1H), 2.16–2.21 (m, 1H), 2.24–2.34 (m, 3H), 2.65–2.72 (m, 2H), 4.24 (ddd, *J*=10.3, 6.2, 2.8 Hz, 1H), 5.12 (dd, *J*=16.8, 1.4 Hz, 1H), 5.13 (dd, *J*=10.8, 1.4 Hz, 1H), 5.67–5.77 (m, 1H), 9.68 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 12.9 (q), 34.4 (t), 34.8 (t), 36.8 (t), 40.8 (d), 43.2 (d), 82.1 (d), 118.1 (t), 134.1 (d), 175.7 (s), 203.4 (d).

4.10. (4*R*,5*S*)-4-Allyl-5-[(2*S*)-2-methyl-3-butynyl]dihydrofuran-2(3*H*)-one[3] 6

To a solution of diethyl(diazomethyl)phosphonate (81 mg, 0.54 mmol) in THF (6 mL), cooled to −78 °C under N_2, was added *t*-BuOK (0.52 mL, 0.52 mmol, 1 M in THF). The reaction mixture was stirred at −78 °C for 15 min and then a solution of the aldehyde (70 mg, 0.35 mmol) in THF (2 mL) was added dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min and quenched with a 1:1 mixture of a saturated NH_4Cl solution and H_2O, extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (20% AcOEt/Hex) to afford 60 mg (89%) of **6** as a colorless oil. $[\alpha]_D^{23}$ −0.13 (*c* 0.42, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ: 1.25 (d, *J*=6.9 Hz, 3H), 1.77 (ddd, *J*=14.2, 6.6, 4.8 Hz, 1H), 1.93 (ddd, *J*=14.2, 7.4, 6.6 Hz, 1H), 2.10 (d, *J*=2.4 Hz, 1H), 2.13–2.21 (m, 1H), 2.24–2.36 (m, 3H), 2.65–2.72 (m, 2H), 4.35 (ddd, *J*=7.4, 4.8, 4.8 Hz, 1H), 5.10–5.15 (m, 2H), 5.69–5.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2 (q), 22.2 (d), 34.2 (t), 37.0 (t), 40.1 (d), 40.9 (t), 69.2 (d), 82.4 (d), 87.6 (s), 118.1 (t), 134.2 (d), 176.1 (s). MS (ESI) *m*/*z*: 215 (M^++Na).

4.11. (3a*R*,7*S*,8a*S*)-7-Methyl-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one[3] 20

To a solution of Grubbs second-generation catalyst (14 mg, 0.016 mmol) in CH_2Cl_2 (52 mL) was added a solution of **6** (60 mg, 0.31 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 12 h and then the solvent was removed in vacuo to give a crude product, which was purified by silica gel column chromatography (10% AcOEt/Hex) to afford 51 mg (85%) of **20** as a pale yellow oil, which upon prolonged sitting formed colorless needles. Mp 56–61 °C. $[\alpha]_D^{23}$ −40.0 (*c* 0.050, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (d, *J*=7.6 Hz, 3H), 1.75 (ddd, *J*=12.4, 12.4, 4.0 Hz, 1H), 2.02–2.18 (m, 2H), 2.28–2.38 (m, 2H), 2.47 (dd, *J*=16.4, 8.8 Hz, 1H), 2.60 (dd, *J*=16.4, 6.0 Hz, 1H), 3.03–3.10 (m, 1H), 4.36 (ddd, *J*=11.6, 8.8, 2.8 Hz, 1H), 4.97 (d, *J*=11.0 Hz, 1H), 5.19 (d, *J*=17.3 Hz, 1H), 5.78 (dd, *J*=9.3, 2.8 Hz, 1H), 6.23 (dd, *J*=17.3, 11.0 Hz, 1H).

4.12. (3*S*,3a*R*,7*S*,8a*S*)-3,7-Dimethyl-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one[8c] 5

To a solution of **20** (40 mg, 0.21 mmol) in THF (2 mL), cooled to −78 °C under N_2, was added LDA (0.30 mL, 0.21 mmol, 0.70 M), prepared with diisopropylamine (0.74 mL, 5.3 mmol) and *n*-BuLi (2.0 mL, 5.0 mmol, 2.5 M in hexane) in THF (5 mL). The reaction mixture was stirred at −78 °C for 1 h and then freshly distilled iodomethane (0.030 mL, 0.25 mmol) was added. The mixture was stirred at −78 °C for 20 min, stirred at 0 °C for 1 h, and then quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with AcOEt and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (10% AcOEt/Hex) to afford 38 mg (90%) of **5** as colorless prisms. Mp 82.5–83.5 °C. $[\alpha]_D^{23}$ −103.1 (*c* 0.32, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) *δ*: 1.13 (d, *J*=7.8 Hz, 3H), 1.22 (d, *J*=7.8 Hz, 3H), 1.70 (ddd, *J*=12.6, 12.6, 3.6 Hz, 1H), 2.07–2.16 (m, 2H), 2.28–2.34 (m, 2H), 2.69 (dq, *J*=7.8, 7.8 Hz, 1H), 3.07 (ddq, *J*=7.8, 4.2, 4.2 Hz, 1H), 4.53 (ddd, *J*=12.6, 10.2, 3.0 Hz, 1H), 4.96 (d, *J*=10.8 Hz, 1H), 5.17 (d, *J*=17.4 Hz, 1H), 5.81 (dd, *J*=9.6, 3.6 Hz, 1H), 6.23 (dd, *J*=17.4, 10.8 Hz, 1H).

4.13. (3a*R*,7*S*,8a*S*)-7-Methyl-3-methylene-6-vinyl-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one[8c] 23

To a solution of **5** (25 mg, 0.12 mmol) in THF (1.2 mL), cooled to −78 °C under N_2, was added LDA (0.26 mL, 0.18 mmol, 0.70 M), prepared with diisopropylamine (0.74 mL, 5.3 mmol) and *n*-BuLi (2.0 mL, 5.0 mmol, 2.5 M in hexane) in THF (5 mL). The reaction mixture was stirred at −78 °C for 20 min and then diphenyl diselenide (75 mg, 0.24 mmol) and HMPA (0.046 mL, 0.24 mmol) were added. The mixture was stirred at −78 °C for 5 min, warmed to −40 °C, and stirred for 2 h. H_2O_2 solution of 30% (0.27 mL, 2.4 mmol) and acetic acid (0.014 mL, 0.24 mmol) were added at −40 °C and then the reaction mixture was stirred at 0 °C for 3 h, quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with AcOEt, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (10% AcOEt/Hex) to afford 20 mg (82%) of **23** as colorless needles. Mp 77.2–77.7 °C (Hex). $[\alpha]_D^{23}$ −40.0 (*c* 0.050, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) *δ*: 1.14 (d, *J*=7.8 Hz, 3H), 1.83 (ddd, *J*=12.6, 12.6, 3.6 Hz, 1H), 2.14 (ddd, *J*=16.2, 11.4, 3.6 Hz, 1H), 2.35 (ddd, *J*=13.2, 4.2, 3.6 Hz, 1H), 2.51–2.56 (m, 1H), 2.67 (ddd, *J*=16.2, 9.0, 2.4 Hz, 2H), 3.11 (dq, *J*=3.6, 3.6 Hz, 1H), 4.29 (ddq, *J*=12.6, 10.2, 2.4 Hz, 1H), 4.99 (d, *J*=10.8 Hz, 1H), 5.20 (d, *J*=17.4 Hz, 1H), 5.45 (d, *J*=3.0 Hz, 1H), 5.84 (dd, *J*=9.0, 3.0 Hz, 1H), 6.18 (d, *J*=3.0 Hz, 1H), 6.26 (dd, *J*=17.4, 10.8 Hz, 1H).

4.14. (−)-Xanthatin (1)[8c]

To a solution of **23** (15 mg, 0.073 mmol) in CH_2Cl_2 (14 mL) was added the second-generation Hoveyda–Grubbs catalyst (**22**, 3.9 mg, 0.0073 mmol) and freshly distilled methyl vinyl ketone (107 mg, 1.5 mmol). The reaction mixture was stirred at 45 °C for 1 h and then the solvent was removed in vacuo to give a crude product, which was purified by silica gel column chromatography (30% AcOEt/Hex) to afford 16 mg (85%) of **1** as colorless needles. Mp 112.3–113.0 °C (Et_2O/Hex). $[\alpha]_D^{25}$ −16.8 (*c* 0.35, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) *δ*: 1.17 (d, *J*=7.8 Hz, 3H), 1.86 (ddd, *J*=12.6, 12.6, 3.6 Hz, 1H), 2.22 (ddd, *J*=12.6, 9.6, 3.6 Hz, 1H), 2.31 (s, 3H), 2.38 (ddd, *J*=12.6, 4.2, 2.4 Hz, 1H), 2.53–2.58 (m, 1H), 2.80 (ddd, *J*=16.2, 8.4, 2.4 Hz, 1H), 3.09 (ddq, *J*=8.4, 4.2, 4.2 Hz, 1H), 4.30 (ddd, *J*=12.6, 9.6, 2.4 Hz, 1H), 5.49 (d, *J*=3.0 Hz, 1H), 6.20 (d, *J*=16.2 Hz, 1H), 6.21 (d, *J*=3.0 Hz, 1H), 6.29 (dd, *J*=9.6, 2.4 Hz, 1H), 7.08 (d, *J*=16.2 Hz, 1H).

4.15. 11,13-Dihydroxanthatin (2)[8c]

To a solution of **5** (20 mg, 0.097 mmol) in CH_2Cl_2 (19 mL) was added the second-generation Hoveyda–Grubbs catalyst (**22**, 7.0 mg, 0.011 mmol) and freshly distilled methyl vinyl ketone (135 mg, 1.9 mmol). The reaction mixture was stirred at 45 °C for 2 h and then the solvent was removed in vacuo to give a crude product, which was purified by silica gel column chromatography (30% AcOEt/Hex) to afford 21 mg (87%) of **2** as colorless needles. Mp 121.0–124.0 °C (CH_2Cl_2/hexane). $[\alpha]_D^{23}$ −75.0 (*c* 0.32, $CHCl_3$). ^1H NMR ($CDCl_3$, 600 MHz) *δ*: 1.15 (d, *J*=7.8 Hz, 3H), 1.23 (d, *J*=7.8 Hz, 3H), 1.72 (ddd, *J*=12.6, 12.6, 3.6 Hz, 1H), 2.13 (dddd, *J*=12.6, 12.6, 7.8, 2.4 Hz, 1H), 2.21 (ddd, *J*=12.0, 12.0, 3.0 Hz, 1H), 2.30 (s, 3H), 2.35 (ddd, *J*=12.6, 4.2, 4.2 Hz, 1H), 2.45 (ddd, *J*=16.2, 9.0, 2.4 Hz, 1H), 2.72 (dq, *J*=7.8, 7.8 Hz, 1H), 3.05 (ddq, *J*=7.8, 4.2, 4.2 Hz, 1H), 4.54 (ddd, *J*=12.6, 10.8, 3.0 Hz, 1H), 6.18 (d, *J*=16.2 Hz, 1H), 6.25 (dd, *J*=9.6, 3.0 Hz, 1H), 7.05 (d, *J*=16.2 Hz, 1H).

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Supplementary data

A supplementary data file (^1H and ^{13}C NMR) of the synthesized compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.077.

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