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BIMETALLIC LEWIS ACID TEMPLATE-MEDIATED ENANTIO-SELECTIVE HETERO-DIELS-ALDER REACTIONS OF 4-SILOXY-2,4-PENTADIENOLS

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Abstract – Enantioselective hetero-Diels-Alder reactions catalyzed by a bimetallic Lewis acid template are described. The hetero-Diels-Alder reactions of 4-siloxy-2,4-pentadienols and various dienophiles by the chiral *H*$_8$-BINOL template provide a general entry into the substituted dihydropyrans with good enantioselectivities. This protocol is also applicable to a dihydropirazine formation.

The highly functionalized tetrahydropyrans are frequently occurring structural motifs in biologically active natural products, including bryostatins,[1,2] laulimalide,[3] and exiguolide[4] (Figure 1). The biological

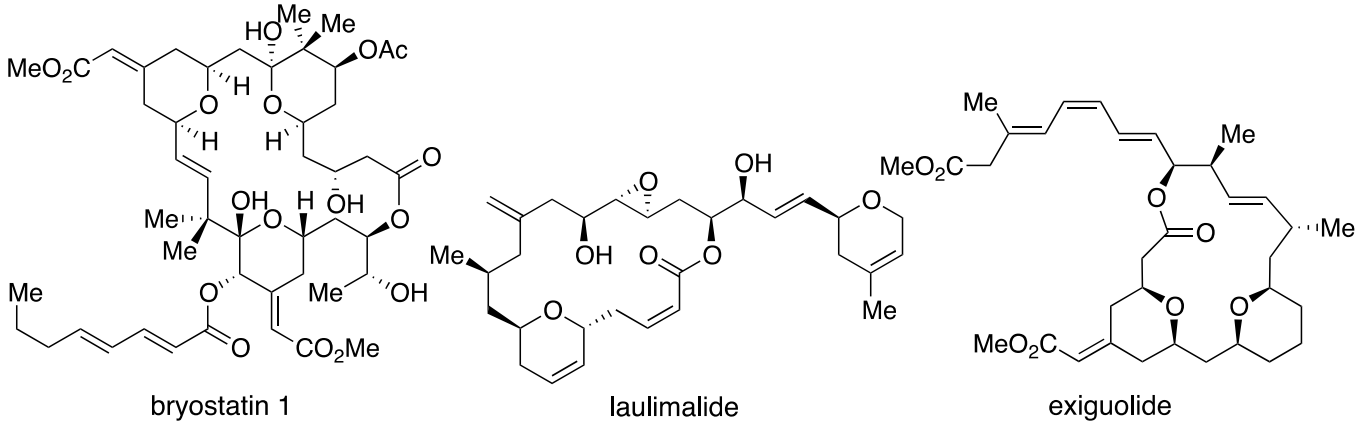

Figure 1. Biologically active natural products containing substituted dihydropyrans

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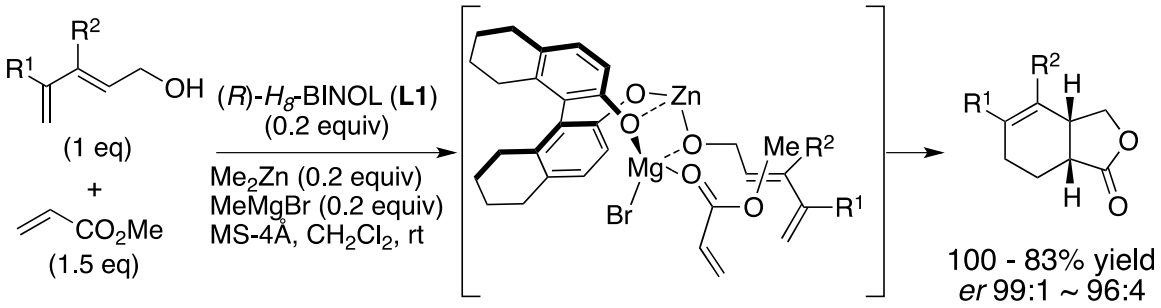
Dedicated with respect to Dr. Tohru Fukuyama on the occasion of his 70th birthday

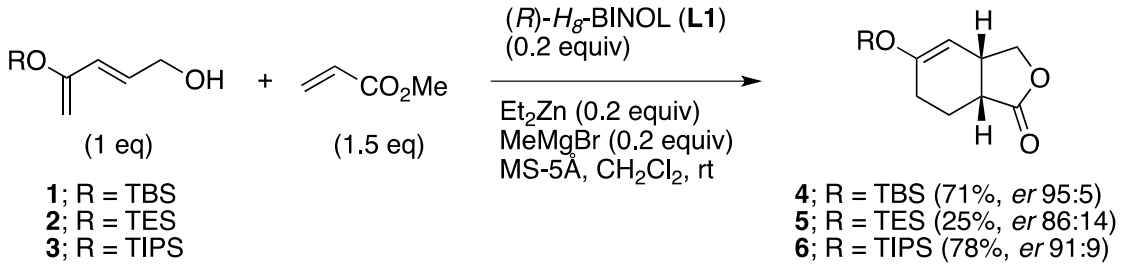
studies of these natural products have indicated antitumor properties and imply an important role in chemical transduction of cell morphology and cellular transport phenomena. Therefore, the development of new methods for the stereoselective construction of the substituted tetrahydropyrans has been important in the creation of useful drugs and other chemical entities. The hetero-Diels-Alder (HDA) reactions are reliable for the stereoselective construction of tetrahydropyrans,[5,6] and effective asymmetric HDA reactions providing the dialkylated tetrahydropyrans have been developed by Jacobsen *et al.*,[7] Wessjohann *et al.*,[8] Hashimoto *et al*.[9] and Terada *et al*.[10]

Recently, we found the bimetallic Lewis acid template-catalyzed asymmetric Diels-Alder reaction of dienols with methyl acrylate in the presence of molecular sieves 4Å or 5Å (MS-4Å or MS-5Å) provides the highly functionalized bicyclic γ-lactones in high selectivity (Scheme 1).[11] In this reaction, methylzinc dienoxide and magenesium binaphthoxide were separately prepared, followed by mixing both complexes to generate the bimetallic Lewis acid template.[12,13] This method is highly practical in terms of yield, enantioselectivity, and mild reaction conditions. Herein we report the Lewis acid template-mediated hetero-Diels-Alder reaction provides *cis*-2,6-dihydropyrans in good selectivities.



Scheme 1. Lewis acid template-catalyzed Diels-Alder reaction of 2,3-pentadienol and methyl acrylate

We first examined the Diels-Alder reaction of 4-siloxy-2,4-pentadienols (**1**-**3**) and methyl acrylate (Scheme 2). The dienols are readily available from ethyl glycolate in 3 steps based on Romo's protocol.[14] Same as our previous works, the use of in situ generated Zn(II)/Mg(II)-(*R*)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthoate (*H*$_8$-BINOL, **L1**) template together with MS-5Å in CH_2Cl_2 at room temperature was found to effectively catalyze the asymmetric Diels-Alder reaction. The reactions of TBS-protected compound **1** and TIPS-protected compound **3** successfully afforded bicyclic lactones **4** and **6**, respectively, in good yields with high enantioselectivities (71%, *er* 95:5 for **4** and 78%, *er* 91:9 for **6**).[15] Whereas compound **2** protected by a TES group suffered its partial desilylation under the conditions, producing **5** in 25% yield and moderate enantioselectivity (*er* 86:14). The absolute stereochemistry of **6** was determined by the chiral HPLC analysis in comparison of the known data.[14]



Scheme 2. Lewis acid template-catalyzed Diels-Alder reaction utilizing 4-siloxy-2,4-pentadienol

We next turned our attention to the hetero-Diels-Alder reaction mediated by Lewis acid templates. At first, the screening of ligands was carried out to find the suitable bimetallic template for HDA reaction. The chiral biaryl ligands (**L1**-**L8**) listed in Figure 2 were tested. Substituted ligands, 3,3'-diphenyl-5,5',6,6', 7,7',8,8'-octahydro-1,1'-bi-2-naphthol (**L2**) was prepared by Blanchet's method,[16] and 3,3'-bis(morpholinomethyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (**L3**) was synthesized according to Pu. [17]

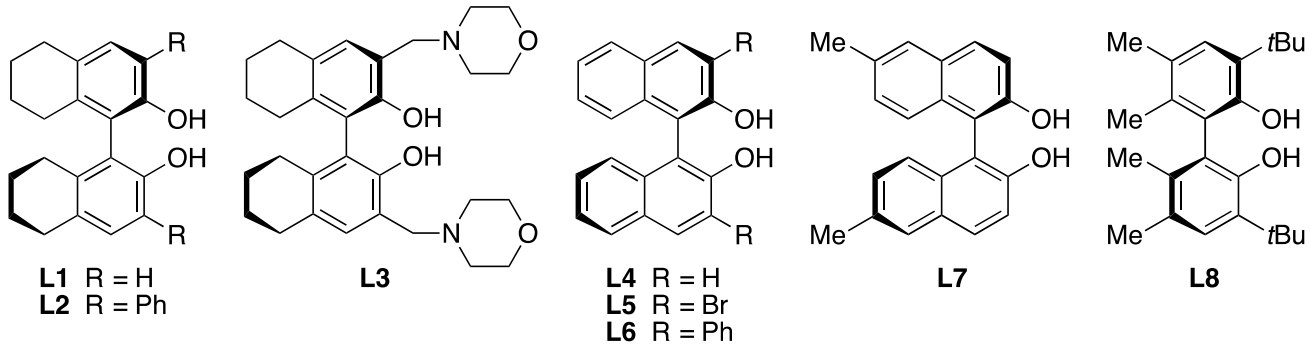
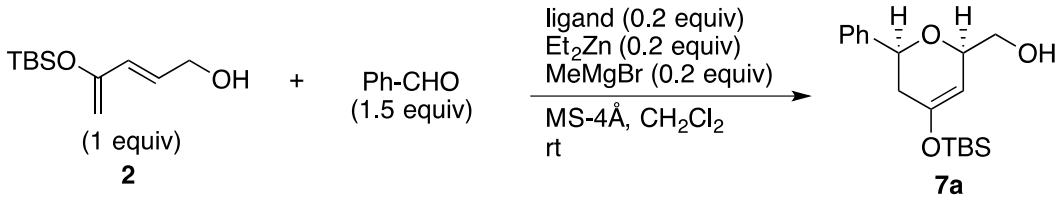


Figure 2. Chiral biaryl ligands for bimetallic Lewis acid templates

The reaction of **1** and benzaldehyde mediated by *H*$_8$-BINOL (**L1**) at room temperature for 3 days generated *cis*-substituted dihydropyran **7a** in 76% yield with an enantiomeric ratio of 89:11 as a single product (entry 1).[18] When bulky 3,3'-diphenyl-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (**L2**) was used in place of **L1**, the HDA reaction proceeded smoothly to afford **7a** in 83% yield; however, the enantioselectivity became very poor (entry 2). On the other hand, the reaction using (*R*)-3,3'-bis(morpholinomethyl)-5,5',6,6',7,7',8, 8'-octahydro-1,1'-bi-2-naphthol (**L3**) gave **7a** with 83:17 *er*, but the reaction yield was low (entry 3). Comparing to **L1**, BINOL (**L4**) and substituted BINOLs (**L5**, **L6**, and **L7**) markedly diminished both the yield and enantioselectivity (entries 4-7), and highly substituted chiral biphenol **L8** was inadequate for asymmetric induction. Consequently, the use of simple *H*$_8$-BINOL (**L1**) was found to effectively promote the high asymmetric induction of the HDA reaction.

Table 1. Examination of chiral diol for Lewis acid template catalyst



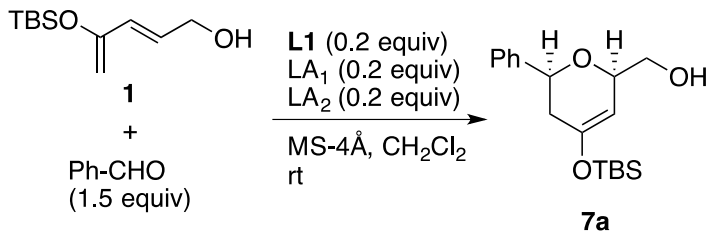
Entry	Ligand	Time	Yield (%)[a)]	*er*[b)]
1	**L1**	3 d	76	89:11
2	**L2**	2 d	83	51:49
3	**L3**	2 d	22	83:17
4	**L4**	2 d	61	66:34
5	**L5**	3 d	83	64:36
6	**L6**	2 d	47	59:41
7	**L7**	2 d	45	69:31
8	**L8**	2 d	56	48:52

a) Determined by ^{1}H-NMR analysis.
b) Er was determined by Chiralpak AD-H.

A brief screening of combination of Lewis acids was also examined (Table 2). The reaction using diethylaluminium chloride in place of methylmagnesium chloride was fruitless (entry 2). In case of trimethylaluminium, the HDA reaction was slow, generating tetrahydropyran **7a** in 18% yield and poor enantioselectivity (entry 3).

Concerning the solvent, apart from CH_2Cl_2, PhMe and THF turned out to be unsuitable for this asymmetric cycloaddtion.

Table 2. Hetero-Diels-Alder reaction mediated by Lewis acid template



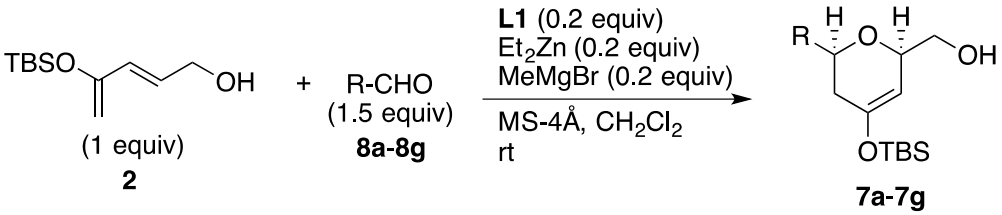
Entry	LA_1	LA_2	Yield (%)[a)]	*er*[b)]
1	MeMgBr	Et_2Zn	76	89:11
2	Et_2AlCl	Et_2Zn	decomp	-
3	MeMgBr	Me_3Al	18	56:44

a) Determined by ^{1}H-NMR analysis.
b) Er was determined by Chiralpak AD-H.

A variety of aldehydes were investigated to explore the generality of this protocol (Table 3). The reaction of 4-chlorobenzaldehyde (**8b**) and 4-ntirobenzaldehyde (**8c**) proceeds faster than benzaldehyde (**8a**) to

afford dihydropyrans in good yields. In these cases, low temperature did not improve the enantioselectivity. In contrast, the HDA reaction of electron-donating aldehydes, 4-methoxybenzaldehyde (**8d**) and 4-tolualdehyde (**8e**), were rather sluggish to give **7d** and **7e** in moderate yields and low enantioselectivities. On the other hand, the reaction of aliphatic aldehydes, such as **8f** and **8g**, resulted in dihydropyrans **7f** and **7g** in 67% yield and 71% yield, respectively but poor enantioselectivity.

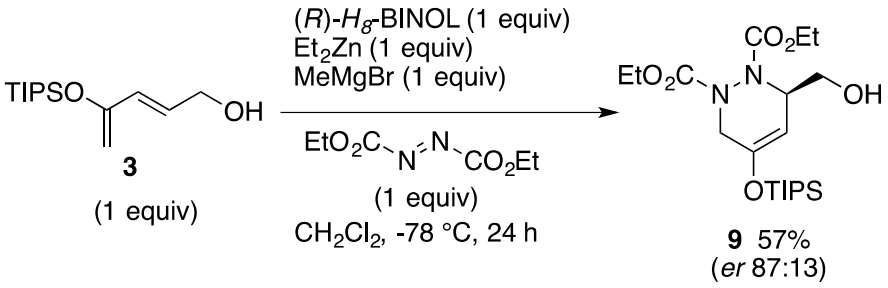
Table 3. Hetero-Diels-Alder reaction mediated by Lewis acid template.



Entry	R	Time	7	Yield (%)[a)]	*er*[b)]
1	C_6H_5 (**8a**)	48 h	**7a**	61	89:11
2	4-ClC_6H_4 (**8b**)	26 h	**7b**	80	66:34
3	4-$NO_2C_6H_4$ (**8c**)	13 h	**7c**	83	68:32
4	4-$MeOC_6H_4$ (**8d**)	180 h	**7d**	55	60:40
5	4-MeC_6H_4 (**8e**)	72 h	**7e**	44	58:42
6	$PhCH_2CH_2$ (**8f**)	48 h	**7f**	67	61:39
7	$TBSOCH_2CH_2$ (**8g**)	69 h	**7g**	51	62:38

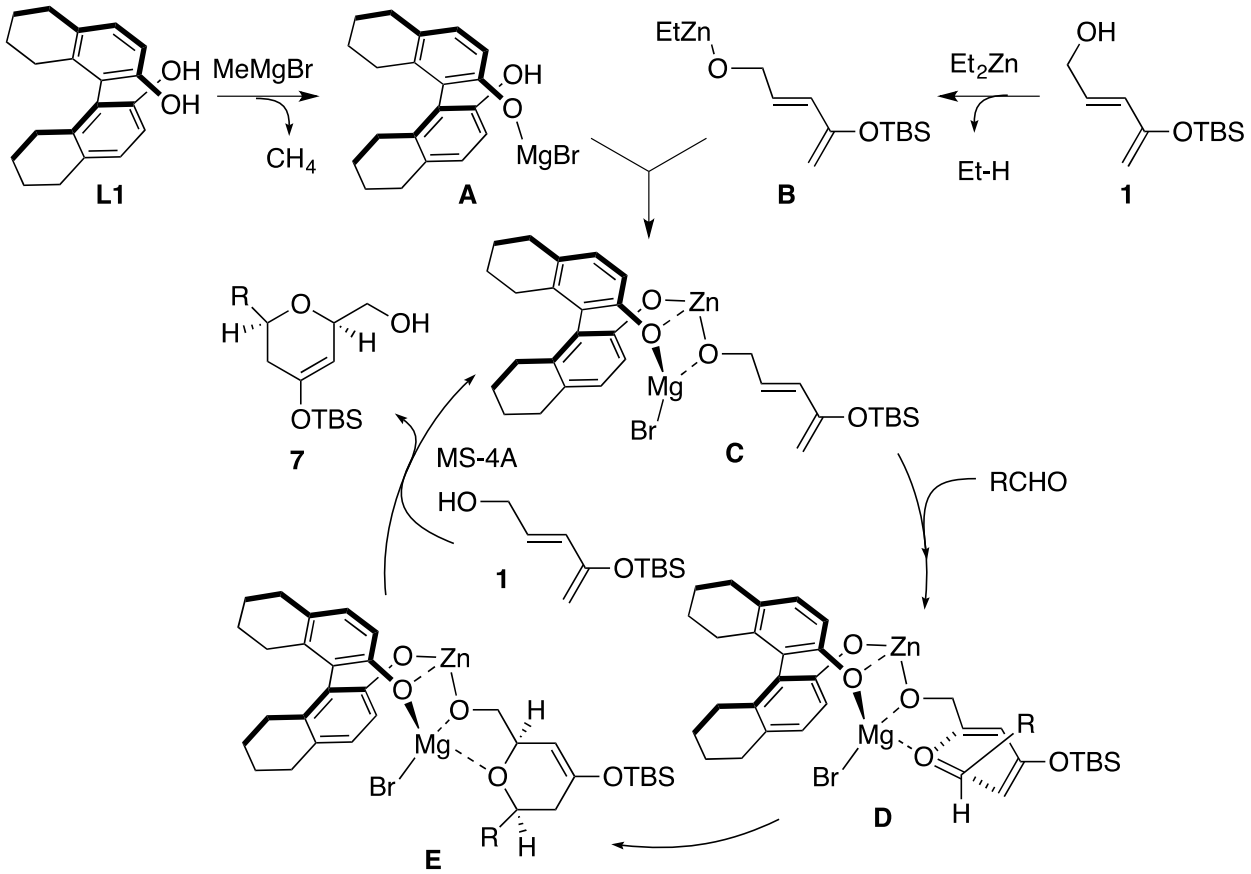
a) Determined by ^{1}H-NMR analysis.
b) Er was determined by Chiralpak AD-H.

To illustrate the application of the HDA to dihydropirazine formation,[19,20] diethyl azodicarboxylate (DEAD) was subjected to the reaction of **3** (Scheme 3). The HDA reaction of **3** and DEAD without Lewis acid template was proved to proceed at room temperature. We examined the reaction at low temperature, whereas the reaction was rather slow and its enantiomeric ratio was 67:33. Finally it turned out that the HDA in the presence of stoichiometric amount of Lewis acid template provided dihydropirazine **9** in 57% yield with an enantiomeric ratio of 87:13. The absolute stereochemistry of dihydropirazine **9** was determined by the comparison of the known compound[20] and the absolute configuration of **7a**-**7g** is proposed on the basis of the HDA reaction of **9**.



Scheme 3. Formation of dihydropirazine by the Lewis acid template-mediated hetero-Diels-Alder reaction

A plausible mechanism for the catalytic tethered Diels-Alder reaction is depicted in Scheme 5. As Ward's LACASA-DA mechanism,[12] magnesium octahydrobinaphthoate **A** and zinc dienolate **B** would form bimetallic Lewis acid **C**, which coordinates with aldehydes to afford self-assembled intermediate **D**. The tethered intermediate **D** undergoes hetero-Diels-Alder reaction (**E**). The ligand exchange of **E** with aldehyde **1** would release dihydropyran **7**. The molecular sieves would play an important role for the ligand substitution to accelerate the catalytic cycle.



Scheme 4. Plausible mechanism of Lewis acid template-catalyzed hetero-Diels-Alder reaction

In conclusion, we have developed the hetero-Diels-Alder reactions of a 4-siloxy-2,4-pentadienol and a dienophile catalyzed by the chiral Lewis acid *H*$_8$-BINOL template. The method allows an expeditious access to chiral dihydropyrans and dihydropirazines which are important for the synthesis of complex natural products. Further exploration of this chemistry is underway in our laboratory.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane (CH_2Cl_2), toluene, and triethylamine (NEt_3) were distilled from CaH_2. Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flash). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^{1}H-NMR (300 and 400 MHz) and ^{13}C-NMR (75 and 100 MHz) spectra were measured using $CDCl_3$, or C_6D_6 as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, 1H; 77.0 ppm, ^{13}C), C_6D_6 (7.13 ppm, 1H; 128.6 ppm, ^{13}C). Mass (MS) and high resolution mass (HRMS) spectra were taken in EI or FAB mode.

(3a*S*,7a*R*)-5-(*tert*-Butyldimethylsilyloxy)-3,3a,7,7a-tetrahydroisobenzofuran-1(6*H*)-one (4). To a solution of **1** (214 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added diethylzinc (1.0 M in hexane; 0.2 mL, 0.2 mmol) at 0 °C and a mixture was stirred for 30 min. In another vessel, MeMgBr (3.0 M in Et_2O; 0.067 mL, 0.2 mmol) was added to a mixture of (*R*)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (**L1**) (58.9 mg, 0.2 mmol) and dried MS-5Å powder (215 mg) in CH_2Cl_2 (1.0 mL) at 0 °C, and the mixture was stirred for 30 min. The former mixture and washings with CH_2Cl_2 (1.6 mL) were added to the latter one, and stirring was continued for 30 min. The combined mixture was diluted with CH_2Cl_2 (2.4 mL) and methyl acrylate (0.135 mL, 1.5 mmol) was added, and stirring was continued at rt for 24 h. The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and filtered through Celite. The filtrate was extracted with AcOEt (100 mL x 3), dried, concentrated and the residue was subjected to chromatography (SiO_2 20 g, hexane–AcOEt, 10:1) to afford compound **4** (190.9 mg, 71%) as white crystals. Mp 86-88 °C; $[\alpha]_D^{20}$ -104.2 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, br), 4.35 (1H, dd, *J* = 8.6, 6.4 Hz), 4.01 (1H, dd, *J* = 8.6, 2.4 Hz), 3.16 (1H, br), 2.74-2.77 (1H, m), 2.05-2.19 (2H, m), 1.93-1.98 (2H, m), 0.92

(9H, s), 0.14 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.3, 153.5, 135.3, 102.8, 100.5, 73.0, 37.5, 35.3, 25.6, 20.4, 17.9, 4.6; FTIR (neat) 2937, 1744, 1658, 1464, 1371, 1195, 1158, 966, 910, 832, 779 cm^{-1}; MS (ESI) *m/z* 291 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{14}H_{24}NaO_3Si$ [$(M+Na)^+$] 291.1392, found 291.1350.

(3a*S*,7a*R*)-5-((Triethylsilyloxy)-3,3a,7,7a-tetrahydroisobenzofuran-1(6*H*)-one (5). Colorless oil; $[\alpha]_D^{31}$ -130.9 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.80 (1H, br), 4.37 (1H, dd, *J* = 8.8, 6.0 Hz), 4.03 (1H, dd, *J* = 8.8, 2.0 Hz), 3.18 (1H, br), 2.72-2.80 (1H, m), 2.14-2.22 (2H, m), 1.96-2.03 (1H, m), 1.84-1.91 (1H, m), 1.00 (9H, t, *J* = 8.0 Hz), 0.68 (6H, q, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.3, 153.5, 99.1, 73.0, 37.5, 35.4, 25.9, 20.5, 6.6, 5.0; FT-IR (neat) 3526, 2954, 1773, 1664, 1457, 1372, 1200, 1007, 912, 850, 742 cm^{-1}; MS (EI) *m/z* 219 (100) 269 (M^+); HRMS (FAB) calcd for $C_{14}H_{25}O_3Si$ [$(M+H)^+$] 269.1573, found 269.1564.

(3a*S*,7a*R*)-5-(Triisopropylsilyloxy)-3,3a,7,7a-tetrahydroiso-benzofuran-1(6*H*)-one (6). Colorless oil; $[\alpha]_D^{31}$ -107.9 (*c* 0.65, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, br), 4.33 (1H, dd, *J* = 8.8, 6.4 Hz), 3.99 (1H, dd, *J* = 8.8, 2.0 Hz), 3.15 (1H, br), 2.73-2.77 (1H, m), 2.14-2.21 (2H, m), 1.97-2.05 (1H, m), 1.80-1.88 (1H, m), 1.09-1.18 (3H, m), 1.06 (18H, d, *J* = 9.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.4, 153.7, 102.0, 73.0, 60.3, 37.5, 35.4, 26.0, 17.9, 12.6 cm^{-1}; FT-IR (neat) 3528, 2962, 1780, 1664, 1464, 1373, 1218, 1076, 1003, 884, 756, 683, 511 cm^{-1}; MS (ESI) *m/z* 333 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{17}H_{30}NaO_3Si$ [$(M+Na)^+$] 333.1862, found 333.1837.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-phenyl-2*H*-pyran (7a). To a solution of **1** (214 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added diethylzinc (1.1 M in toluene; 0.18 mL, 0.2 mmol) at 0 °C and a mixture was stirred for 10 min. In another vessel, MeMgBr (3.0 M in Et_2O; 0.067 mL, 0.2 mmol) was added to a mixture of (*R*)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (58.9 mg, 0.2 mmol) and dried MS-4Å powder (215 mg) in CH_2Cl_2 (1.0 mL) at 0 °C, and the mixture was stirred for 30 min. The former mixture and washings with CH_2Cl_2 (1.6 mL) were added to the latter one, and stirring was continued for 30 min. The combined mixture was diluted with CH_2Cl_2 (2.4 mL) and benzaldehyde (0.15 mL, 1.5 mmol) was added, and stirring was continued at rt for 48 h. The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and filtered through Celite. The filtrate was extracted with AcOEt (100 mL x 3), dried, concentrated. The partial residue was purified by flash chromatography (SiO_2, hexane–AcOEt, 20:1) to afford crude **7a** (143.5 mg). Since compound **7a** was inseparable from starting material **1** and slightly unstable, and the reaction yield was determined to be 76% by ^{1}H-NMR analysis: ^{1}H-NMR (400 MHz, C_6D_6) δ 7.25-7.27 (2H, m), 7.18-7.19 (2H, m), 7.09-7.16 (1H, m), 4.76 (1H, br), 4.47 (1H, dd, *J* = 3.6, 11.0 Hz), 4.28 (1H, br), 3.61 (1H, dd, *J* = 5.2 Hz, 11.0 Hz), 3.55 (1H, dd, *J* = 5.2 Hz, 11.0 Hz), 2.31-2.39 (1H, m), 2.12 (1H, dt, *J* = 16.8, 2.8 Hz), 0.96 (9H, s), 0.12 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.4, 141.6, 128.3, 127.6, 125.8, 102.2, 75.9, 75.5, 66.2, 38.0, 25.5, 17.9, -4.7; FT-IR (neat)

3421, 2933, 2859, 1671, 1462, 1355, 1253, 1197, 1128, 1057, 894, 839, 697 cm^{-1}; MS (ESI) *m/z* 343 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{28}NaO_3Si$ [$(M+Na)^+$] 343.1705, found. 343.1704.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-(4-chlorophenyl)-2*H*-pyran (7b). Colorless oil; $[\alpha]_D^{29}$ -207.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.39 (4H, m), 4.78 (1H, br), 4.66 (1H, dd, *J* = 10.8, 3.0 Hz), 4.45 (1H, br), 3.69-3.74 (1H, m), 3.56-3.61 (1H, m), 2.29-2.36 (1H, m), 2.20 (1H, dt, *J* = 17.2, 3.0 Hz), 1.95 (1H, dd, *J* = 4.6, 7.8 Hz), 0.92 (9H, s), 0.18 (3H, s), 0.16 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.3, 140.3, 133.4, 128.6, 127.3, 102.2, 75.7, 75.4, 66.3, 38.1, 25.7, 18.1, -4.5; FT-IR (neat) 3432, 2935, 1671, 1467, 1361, 1254, 1203, 1082, 897, 841, 692, 555, 460 cm^{-1}; MS (ESI) *m/z* 377 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{27}ClNaO_3Si$ [$(M+Na)^+$] 377.1316, found. 377.1290.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-(4-nitrophenyl)-2*H*-pyran (7c). Colorless oil; $[\alpha]_D^{29}$ -305.5 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (2H, d, *J* = 8.8 Hz), 7.54 (2H, d, *J* = 8.8 Hz), 4.76-4.79 (2H, m), 4.46 (1H, br), 3.69-3.72 (1H, m), 3.61 (2H, dd, *J* = 6.8, 12.0 Hz), 2.25-2.27 (3H, m), 0.90 (9H, s), 0.17 (3H, s), 0.15 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.9, 149.1, 147.3, 126.5, 123.7, 102.0, 75.8, 75.0, 66.2, 37.9, 25.6, 18.0, -4.6; FT-IR (neat) 3420, 3074, 2954, 2249, 1931, 1672, 1603, 1528, 1363, 910, 566, 450 cm^{-1}; MS (ESI) *m/z* 388 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{27}NNaO_5Si$ [$(M+Na)^+$] 388.1556, found. 388.1561.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-(4-methoxyphenyl)-2*H*-pyran (7d). Colorless oil; $[\alpha]_D^{29}$ -2.8 (*c* 0.85, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.8 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 4.78 (1H, br), 4.63 (1H, dd, *J* = 3.2, 10.6 Hz), 4.44 (1H, br), 3.81 (3H, s), 3.68-3.71 (1H, br), 3.57 (1H, dd, *J* = 7.2, 11.2 Hz), 2.35-2.44 (1H, m), 2.18 (1H, dt, *J* = 3.2, 16.4 Hz), 2.07 (1H, br), 0.93 (9H, s), 0.18 (3H, s), 0.17 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.2, 150.6, 133.8, 127.3, 113.8, 102.2, 75.7, 75.5, 66.3, 55.3, 37.9, 37.9, 25.6, 18.0, -4.6; FT-IR (neat) 3437, 2935, 1672, 1614, 1514, 1465, 1361, 1252, 1127, 1036, 898, 842, 564 cm^{-1}; MS (ESI) *m/z* 373 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{19}H_{30}NaO_4Si$ [$(M+Na)^+$] 373.1811, found. 373.1823.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-(4-methylphenyl)-2*H*-pyran (7e). Colorless oil; $[\alpha]_D^{28}$ +7.4 (*c* 0.99, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.0 Hz), 4.78 (1H, br), 4.65 (1H, dd, *J* = 3.2, 10.6 Hz), 4.46 (1H, br), 3.70 (1H, dd, *J* = 2.8, 11.2 Hz), 3.57 (1H, dd, 6.8, 11.2 Hz), 2.35-2.42 (1H, m), 2.22 (3H, s), 2.20 (1H, dt, *J* = 3.2, 16.4 Hz), 2.10 (1H, br), 0.93 (9H, s), 0.18 (3H, s), 0.17 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.5, 138.7, 137.5, 129.1, 125.9, 102.2, 75.9, 75.5, 66.3, 38.0, 25.6, 21.1, 18.0, -4.6; FT-IR (neat) 3437, 2933, 1671, 1514, 1465, 1360, 1254, 1200, 1066, 898, 840, 558 cm^{-1}; MS (ESI) *m/z* 357 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{19}H_{30}NaO_3Si$ [$(M+Na)^+$] 357.1862, found. 357.1873.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-phenethyl-2*H*-pyran (7f). Compound **7f** was purified after removal of the TBS group as a corresponding ketone, (2*R*,6*R*)-tetrahydro-2-(hydroxymethyl)-6-phenethylpyran-4-one: White crystals; Mp 75-77 °C; $[\alpha]_D^{29}$ +2.3 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, C_6D_6) δ 7.26-7.39 (5H, m), 3.77-3.86 (2H, m), 3.66-3.70 (2H, m), 2.79-2.93 (2H, m), 2.44-2.55 (2H, m), 2.34-2.40 (2H, m), 2.22 (1H, br), 2.06-2.15 (1H, m), 1.87-1.96 (1H, m); ^{13}C-NMR (100 MHz, C_6D_6) δ 206.7, 141.2, 128.4, 128.3, 126.0, 76.9, 76.0, 65.3, 47.6, 43.2, 37.6, 31.5; FT-IR (neat) 3435, 3027, 2925, 2861, 1715, 1492, 1333, 1281, 1145, 1060, 848, 750, 701, 524 cm^{-1}; MS (DART) *m/z* 235 $[(M+H)^+]$; HRMS (DART) calcd for $C_{14}H_{19}O_3$ $[(M+H)^+]$ 235.1334, found. 235.1328.

(2*S*,6*R*)-3,6-Dihydro-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)-2-(2-*tert*-butyldimethylsilyl-oxyethyl)-2*H*-pyran (7g). Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, br), 4.22 (1H, br), 3.67-3.79 (3H, m), 3.58 (1H, dd, *J* = 3.2, 11.2 Hz), 3.45 (1H, dd, *J* = 6.8, 11.2 Hz), 2.21 (1H, br), 2.00-2.08 (1H, m), 1.92 (1H, dt, *J* = 3.2, 11.2 Hz), 1.65-1.80 (2H, m), 0.89 (9H, s), 0.87 (9H, s), 0.13 (3H, s), 0.12 (3H, s), 0.03 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.6, 102.2, 74.9, 70.9, 66.1, 59.2, 38.7, 36.4, 25.9, 25.5, 18.2, 17.9, -4.7, -5.4; FT-IR (neat) 3451, 2934, 2861, 1672, 1468, 1361, 1254, 1198, 1096, 908, 836, 778 cm^{-1}; MS (ESI) *m/z* 425 $[(M+Na)^+]$; HRMS (ESI) calcd for $C_{20}H_{42}NaO_4Si_2$ $[(M+Na)^+]$ 425.2519, found. 425.2507.

Diethyl (*R*)-3-(hydroxymethyl)-5-(triisopropylsilyloxy)-pyridazine-1,2(3*H*,6*H*)-dicarboxylate (9). To a solution of **3** (100 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) was added diethylzinc (1.12 M in hexane; 0.34 mL, 0.39 mmol) at 0 °C and a mixture was stirred for 5 min. In another vessel, MeMgBr (3.0 M in Et_2O; 0.12 mL, 0.39 mmol) was added to a mixture of (*R*)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (115 mg, 0.39 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C, and the mixture was stirred for 5 min. The former mixture and washings with CH_2Cl_2 (3.3 mL) were added to the latter one, and stirring was continued for 5 min. The combined mixture was diluted with CH_2Cl_2 (3.3 mL) and diethyl azodicarboxylate (2.2 M in toluene, 0.18 mL, 0.39 mmol) was added at -78 °C, and stirring was continued at rt for 18 h. The reaction mixture was diluted with sat. $NaHCO_3$ (5 mL) and filtered through Celite. The filtrate was extracted with AcOEt (10 mL x 3), washed with brine, dried, concentrated and the residue was subjected to chromatography (SiO_2 25 g, hexane–AcOEt, 3:1) to afford compound **9** (97.8 mg, 0.23 mmol, 58%) as yellow oil; $[\alpha]_D^{30}$ +29.4 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, dd, *J* = 14.4, 4.4 Hz), 4.72 (1H, s, br), 4.30-4.13 (5H, m), 3.84 (0.5H, s, br), 3.72 (0.5H, d, *J* = 16.0 Hz), 3.54 (1H, m), 3.38 (0.5H, t, *J* = 11.6 Hz), 3.28 (0.5H, t, *J* = 11.6 Hz), 1.32-1.25 (6H, m), 1.20-1.10 (2H, m), 1.06-1.03 (18H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.4, 156.3, 155.9, 155.1, 99.7, 98.9, 63.1, 62.9, 62.8, 62.7, 62.3, 61.9, 46.3, 45.0, 17.8, 14.53, 14.48, 14.46, 12.5; FT-IR (neat) 3498, 3303, 2944, 2869, 1712, 1417, 1221, 1061, 887, 441

cm^{-1}; MS (ESI) *m/z* 453 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{20}H_{38}N_2O_6Si$ [$(M+Na)^+$] 453.2397, found 453.2376.

REFERENCES AND NOTES

1. G. R. Pettit, C. L. Herald, D. L. Doubek, D. L. Herald, E. Arnold, and J. Clardy, *J. Am. Chem. Soc.*, 1982, **104**, 6846.
2. For reviews of the bryostatins and bryostatin analogues, see: (a) K. J. Hale, M. G. Hummersome, S. Manaviazar, and M. Frigerio, *Nat. Prod. Rep.*, 2002, **19**, 413; (b) K. J. Hale and S. Manaviazar, *Chem. Asian J.*, 2010, **5**, 704.
3. (a) E. Quinoa, Y. Kakou, and P. Crews, *J. Org. Chem.*, 1988, **53**, 3642; (b) D. G. Corley, R. Herb, R. T. E. Moore, P. J. Scheuer, and V. J. Paul, *J. Org. Chem.*, 1988, **53**, 3644.
4. (a) S. Ohta, M. M. Uy, M. Yanai, E. Ohta, T. Hirata, and S. Ikegami, *Tetrahedron Lett.*, 2006, **47**, 1957; (b) E. A. Crane, T. P. Zabawa, R. L. Farmer, and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2011, **50**, 9112; (c) H. Fuwa, T. Suzuki, H, Kubo, T. Yamori, and M. Sasaki, *Chem. Eur. J.*, 2011, **17**, 2678; (d) H. Fuwa, K. Mizunuma, M. Sasaki, T. Suzuki, and H. Kubo, *Org. Biomol. Chem.*, 2013, **11**, 3442.
5. For a recent review on enantioselective HDA reactions, see: (a) K. A. Jørgensen in Cycloaddition Reactions in Organic Synthesis, ed. by S. Kobayashi and K. A. Jørgensen, Wiley-VCH, Weinheim, 2002, chap. 4; b) H. Pellissier, *Tetrahedron*, 2009, **65**, 2839.
6. For selected examples of catalytic, enantioselective HDA reactions, see: (a) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1986, **108**, 7060; (b) K. A. Jørgensen, *Angew. Chem. Int. Ed*., 2000, **39**, 3558; (c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668 ; (d) Y. Huang, A. K. Unni, A. N. Thadani, and V. H. Rawal, *Nature*, 2003, **424**, 146; (e) M. P. Doyle, M. Valenzuela, and P. Huang, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5391; (f) L. Lin, Y. Kuang, X. Liu, and X. Feng, *Org. Lett.*, 2011, **13**, 3868; (g) J. Guin, C. Rabalakos, and B. List, *Angew. Chem. Int. Ed.*, 2012, **51**, 8859; (h) L. Liu, H. Kim, Y. Xie, C. Farès, P. S. J. Kaib, R. Goddard, and B. List, *J. Am. Chem. Soc.*, 2017, **139**, 13656.
7. (a) E. N. Jacobsen, A. G. Dossetter, and T. F. Jamison, *Angew. Chem. Int. Ed.*, 1999, **38**, 2398; (b) C. F. Thompson, T. F. Jamison, and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 9974.
8. E. Ruijter, H. Schültingkemper, and L. A. Wessjohann, *J. Org. Chem.*, 2005, **70**, 2820.
9. M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro, and S. Hashimoto, *Angew. Chem. Int. Ed.*, 2004, **43**, 2665.
10. N. Momiyama, H. Tabuse, and M. Terada, *J. Am. Chem. Soc.*, 2009, **131**, 12882.
11. J. Ishihara, S. Nakadati, Y. Watanabe, and S. Hatakeyama, *J. Org. Chem.*, 2015, **80**, 2037.

12. For Lewis acid template reaction, see: (a) D. E. Ward and M. S. Abaee, *Org. Lett.*, 2000, **2**, 3937; (b) D. E. Ward and M. S. Souweha, *Org. Lett.*, 2005, **7**, 3533.
13. For the review of bimetallic Lewis acid reactions, see: S. Matsunaga and M. Shibasaki, *Chem. Commun.*, 2014, **50**, 1044.
14. M. E. Abbasov, B. M. Hudson, D. J. Tantillo, and D. Romo, *J. Am. Chem. Soc.*, 2014, **136**, 4492.
15. The yield was determined by ^{1}H-NMR analysis using dimethyl sulfone as an internal standard. The enantiomeric excess was determined by chiral HPLC analysis in comparison with authentic racemic material using a Chiralcel OD-H column, λ = 210 nm.
16. G. Pousse, A. Devineau, V. Dalla, L. Humphreys, M.-C. Lasne, J. Rouden, and J. Blanchet, *Tetrahedron*, 2009, **65**, 10617.
17. Y.-C. Qin, L. Liu, M. Sabat, and L. Pu, *Tetrahedron*, 2006, **62**, 9335.
18. The yield was determined by ^{1}H-NMR analysis using dimethyl sulfone as an internal standard. The enantiomeric excess was determined by chiral HPLC analysis of the corresponding ketone after the removal of silyl group by Bu_4NF in comparison with authentic racemic material using a Chiralpak AD-H column, λ □ 254 nm.
19. (a) M. Kawasaki and H. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 16482; (b) B. Liu, T.-Y. Liu, S.-W. Luo, and L.-Z. Gong, *Org. Lett.*, 2014, **16**, 6164; (c) B. Liu, K.-N. Li, S.-W. Luo, J.-Z. Huang, H. Pang, and L.-Z. Gong, *J. Am. Chem. Soc.*, 2013, **135**, 3323.
20. (a) M. J. Alves, F. T. Costa, V. C. M. Duarte, A. G. Fortes, J. A. Martins, and N. M. Micaelo, *J. Org. Chem.*, 2011, **76**, 9584; (b) V. C. M. Duarte, M. J Alves, and A. G. Fortes, *Synlett*, 2014, **25**, 1751.