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An enantioselective synthesis of phomopsolide D

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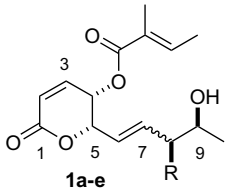
Abstract—A short enantioselective route to the highly functionalized α,β-unsaturated δ-lactone natural product phomopsolide D and three of its stereoisomers, has been accomplished. All of the carbon atoms of phomopsolide D come from tiglic acid and 2-furyl-1-penta-1′,3′-dienylketone (furan plus hexadienal). This approach derives its asymmetry from the sequential use of two catalytic asymmetric reactions; these being a Sharpless dihydroxylation reaction and a Noyori furylketone reduction. The resulting furfuryl alcohols were stereoselectively transformed into α,β-unsaturated δ-lactones via a short highly diastereoselective oxidation and reduction sequence.

1. Introduction

In search of natural compounds that have an effective antiboring/antifeeding activity against the elm bark beetles, Grove,[1] and later Stierle et al.[2] found a series of related 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones, the phomopsolides, with the desired deterrent activity for Scolytid beetles. In 1985, Grove isolated phomopsolide A and B from the fungus *Phomopsis oblonga*, which co-habitates with the elm trees.[1] In 1997, Stierle re-isolated phomopsolide A and B in addition to three new phomopsolides (C–E) from fungi lying in the bark of the Pacific yew (*Taxus brevifolia*) and found them to have antimicrobial activity against *S. aureus*[2] (Fig. 1).

To date two phomopsolides have been synthesized that being phomopsolide B by Noshita et al.[3] and phomopsolide C by us.[4] Our route to phomopsolide C uses our furfuryl alcohol to pyranone methodology.[5–7] While the two previous routes were significant in that they established the relative and absolute stereochemistry of two phomopsolides, both approaches were deemed to be too inefficient to provide sufficient quantities of material for further study.[8] Thus, we desired a more expedient route to the phomopsolides, which had better relative stereocontrol in addition to being amenable to the synthesis of the many possible phomopsolides. Herein we report our successful endeavors toward the first synthesis of phomopsolide D (**1d**).



1a: cis, R = O; **phomopsolide A**
1b: trans, R = OH; **phomopsolide B**
1c: trans, R = O; **phomopsolide C**
1d: 6,7-dihydro, R = OH; **phomopsolide D**
1e: 6,7-dihydro, R = O; **phomopsolide E**

Figure 1. Structures of phomopsolides.

Our previous route targeted the C-6/C-7 *trans*-phomopsolide isomer **1c**, phomopsolide C, from enone **2** (Scheme 1). We opted for a degree of convergence by deriving the C-9 stereochemistry from lactic acid where as the C-4/C-5 stereochemistry would come from our furan to pyranone oxidation strategy. While this route was successful in that for the first time it prepared phomopsolide C (**1c**) and in significantly less steps, the route, however, failed to produce enough material for biological testing.

Because of their purported antimicrobial activity[2] we became interested in the synthesis of the other members of the phomopsolides along with various analogs.[9] As we revisited this class of structures, we were interested in developing a route to the phomopsolides that would control all the stereochemistry via asymmetric catalysis. To satisfy our esthetic concerns and illustrate the biological importance of the C-6/C-7 double bond, we decided to devise an abbreviated synthesis of phomopsolide D. Outlined in Scheme 2 is our second-generation approach to the phomopsolides, specifically phomopsolide D. This

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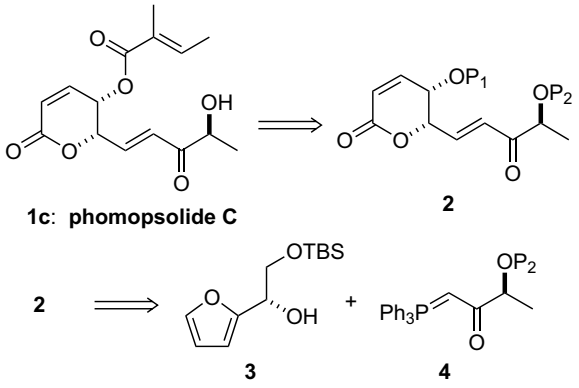
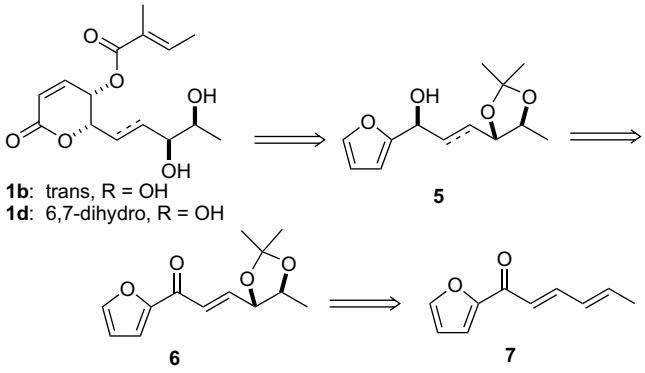


Scheme 1. Retrosynthetic analysis of phomopsolide C.



Scheme 2. Retrosynthetic analysis of phomopsolide B and D.

new route uses both a Sharpless asymmetric dihydroxylation reaction as well as a rare tandem 1,4/1,2-reduction using Noyori catalyst to establish all the absolute and relative stereochemistry (Scheme 2).

This approach started with a two-step addition of 2-furyllithium **9** to hexadienal **8** followed by the MnO_2 oxidation to afford dienone **7** in 84% yield. A regioselective Sharpless asymmetric dihydroxylation reaction of **7** gave diol **10** in excellent unpurified yield.[10] Acetonide protection of crude **10** gave enone **6** in 91% yield from dienoate **7** (Scheme 3).

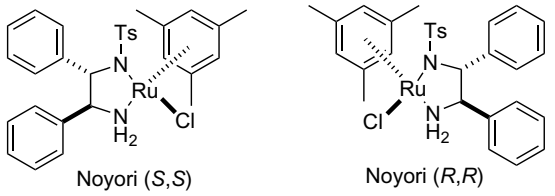
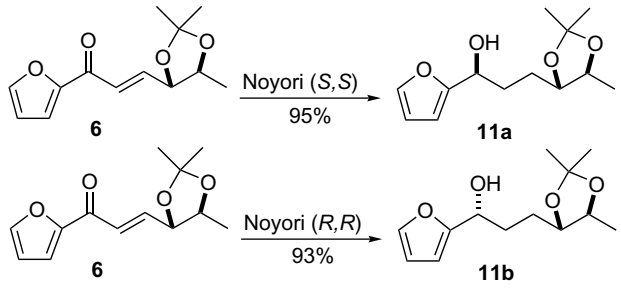


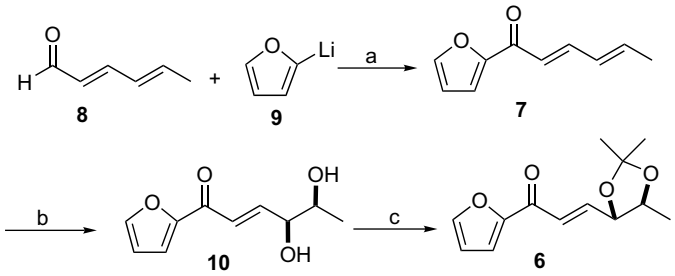
Figure 2. Both enantiomers of Noyori's catalyst.

Exposure of enone **6** to Noyori's catalyst (*S*,*S*)[11] (Fig. 2) in Et_3N/HCO_2H (1:2) led to a highly diastereoselective tandem 1,4/1,2-reduction, providing **11a** in a 95% yield and as a single diastereomer.[12] The 1,4/1,2-reduction selectivity was independent of the relative stereochemistry between substrate and catalyst. Thus when enone **6** was exposed to the Noyori's catalyst (*R*,*R*) an equally diastereoselective tandem 1,4/1,2-reduction occurred providing **11b** in a 93% yield (Scheme 4).[13]

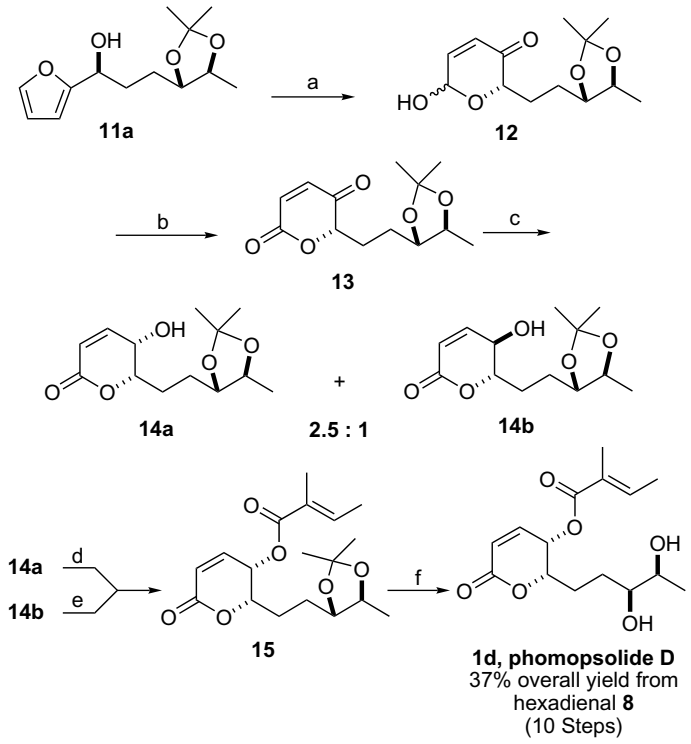
After the Achmatowicz reaction (NBS/H_2O),[14] **11a** was cleanly converted to pyran **12** (89%), which upon Jones oxidation was converted to ketolactone **13**. Ketolactone **13** was reduced under Luche conditions to provide a 2.5:1 ratio of **14a** and **14b**.[15] After chromatographic separation, both diastereomers **14a** and **14b** were converted into the protected phomopsolide D by a DCC coupling or Mitsunobu inversion, providing **15** in 82% and 57% yields, respectively. Acid catalyzed deprotection of **15** gave the natural product phomopsolide D (**1d**) in 90% yield (Scheme 5). Synthetic **1d**'s spectral data matched that of the isolated natural product in terms of IR, ^1H, ^{13}C NMR, and sign of optical rotation.[2,16]



Scheme 4. Noyori asymmetric catalytic hydrogenation of enone **6**.



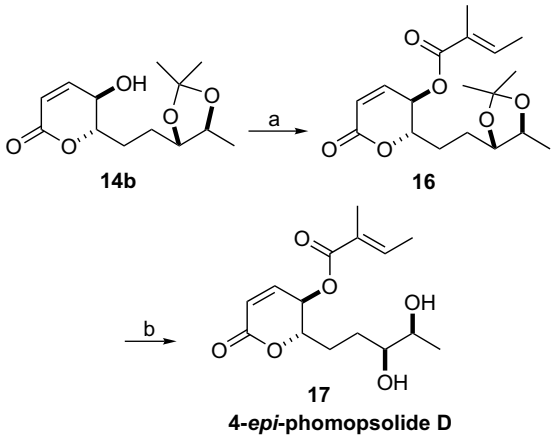
Scheme 3. Reagents and conditions: (a) (i) THF, −78 °C, (ii) MnO_2 (84% in two steps); (b) 1% OsO_4, 2% $(DHQ)_2PHAL$, 3 equiv $K_3Fe(CN)_6$/3 equiv K_2CO_3/1 equiv $MeSO_2NH_2$ in 1:1 *t*-BuOH/H_2O, 0 °C; (c) 2,2-DMP, PPTS (91% in two steps).



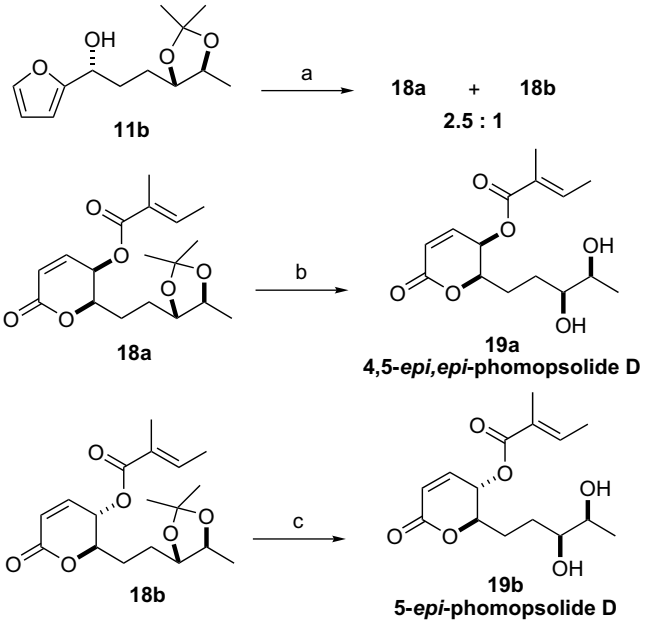
Scheme 5. Reagents and conditions: (a) NBS, THF/H_2O, 0 °C, 89%; (b) Jones reagent (2.98 M), 0 °C, 90%; (c) $NaBH_4$, $CeCl_3$, 0 °C, 95%; (d) tiglic acid, DCC, rt, 82%; (e) tiglic acid, PPh_3/DEAD, 57%; (f) 1 N HCl, MeOH, 90%.

In addition the minor diastereomer **14b** was converted into the protected 4-*epi*-phomopsolide D by a DCC coupling (Scheme 6), providing **16** in 84% yield. Acid catalyzed deprotection of **16** gave the C-4 epimer of phomopsolide D **17** in 92% yield.

Finally by applying the same reaction sequences from Scheme 5 on the furfuryl alcohol **11b**, two more diastereomeric phomopsolides **19a** and **19b** can be prepared (Scheme 7). Thus exposing **11b** to the bis-oxidation (NBS/Jones) then reduction ($NaBH_4$) sequences followed by a DCC coupling reaction afforded a 54% yield of a 2.5:1 ratio of protected isomeric phomopsolides **18a** and **18b**. At this stage **18a** and **18b** were easily separated by silica gel chromatography and deprotected (1 N HCl in MeOH) to afford both the 4,5-*epi*,*epi*-phomopsolide D **19a** and the 5-*epi*-phomopsolide D **19b** in 92% and 91% yields, respectively.



Scheme 6. Reagents and conditions: (a) tiglic Acid, DCC, 84%; (b) 1 N HCl, MeOH, 92%.



Scheme 7. Reagents and conditions: (a) (i) NBS, THF/H_2O, 0 °C, (ii) Jones reagent (2.98 M), 0 °C, (iii) $NaBH_4$, $CeCl_3$, 0 °C, (iv) tiglic acid, DCC (54% in four steps); (b) 1 N HCl, MeOH, 92%; (c) 1 N HCl, MeOH, 91%.

In conclusion, this highly enantio and diastereocontrolled route to phomopsolide D (**1d**) was completed in 10 steps and 37% overall yield.[8] Future work in this area will involve efforts to broaden this route to include the stereoselective preparation of the other phomopsolides.

2. Experimental section

2.1. (1*S*,4*S*,5*S*)-4,5-Isopropylenedioxy-1-(2-furanyl)-hexan-1-ol (11a)

To a 10 mL flask was added enone **6** (236 mg, 1 mmol), formic acid–triethylamine (2:1, 2 mL), and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN·HCl (2.9 mg, 5 μmol). The resulting orange solution was stirred at room temperature for 24 h. The mixture was diluted with water (4 mL) and extracted with EtOAc (3×15 mL). The organic layers were combined, washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (EtOAc/hexane, 2:8) on silica gel yielded alcohol **11a** (228 mg, 95%) as a light yellow oil: R_f (50% EtOAc/hexanes) = 0.67; $[\alpha]_D^{25}$ −25 (*c* 2.18, MeOH); IR (thin film, cm^{-1}) 3425, 2984, 2934, 1380, 1241, 1093, 1006; ^1H NMR (270 MHz, $CDCl_3$): δ 7.34 (d, *J* = 1.7 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 4.71 (ddd, *J* = 7.7, 4.9, 4.7 Hz, 1H), 3.70 (dq, *J* = 8.4, 5.9 Hz, 1H), 3.55 (ddd, *J* = 8.2, 8.1, 3.7 Hz, 1H), 3.00 (d, *J* = 4.7 Hz, 1H), 1.96 (m, 2H), 1.62 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.21 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$): δ 156.6, 141.7, 110.0, 107.9, 105.6, 82.1, 76.6, 67.7, 32.4, 28.3, 27.2, 27.1, 17.3; ESI HRMS calcd for $[C_{13}H_{20}O_4+Na]^+$: 263.1260, found: 263.1261.

2.2. Phomopsolide D (1d)

To a 10 mL round bottom flask was added ester **15** (75 mg, 0.22 mmol), MeOH (4 mL), and HCl (1 N, 1 mL). The reaction mixture was stirred at room temperature for 12 h. Then the solution was extracted with EtOAc (3×15 mL). The organic fractions were combined, washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated. Purification on silica gel (EtOAc/hexane, 3:7) yielded Phomopsolide D (63 mg, 90%) as a colorless oil: R_f (EtOAc) = 0.32; $[\alpha]_D^{25}$ +296 (*c* 1.25, MeOH) [lit.[2] $[\alpha]_D^{25}$ +110 (*c* 0.0045, MeOH)];[16] IR (thin film, cm^{-1}) 3450, 2968, 2928, 1711, 1649, 1257, 1132, 829, 733; ^1H NMR (600 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 9.7, 5.9 Hz, 1H), 6.87 (qq, *J* = 6.9, 1.0 Hz, 1H), 6.16 (d, *J* = 9.7 Hz, 1H), 5.24 (dd, *J* = 5.9, 2.7 Hz, 1H), 4.56 (ddd, *J* = 8.9, 4.5, 2.5 Hz, 1H), 3.56 (dq, *J* = 6.4, 6.2 Hz, 1H), 3.32 (ddd, *J* = 10.2, 6.0, 6.0 Hz, 1H), 2.83 (br/s, 1H), 2.66 (br/s, 1H), 2.04 (m, 2H), 1.80 (s, 3H), 1.78 (d, *J* = 6.7 Hz, 3H), 1.66 (m, 2H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 163.2, 141.0, 139.7, 127.4, 124.6, 78.8, 75.1, 70.6, 62.9, 28.3, 26.3, 19.5, 14.5, 12.0; ESI HRMS calcd for $[C_{15}H_{22}O_6+Na]^+$: 321.1314, found: 321.1322.

2.3. 4-*epi*-Phomopsolide D (17)

The procedure was the same as that for the preparation of Phomopsolide D. Thus ester **16** (72.8 mg, 0.22 mmol) was used to afford 4-*epi*-Phomopsolide D (59.1 mg, 92%) as a colorless oil: R_f (50% EtOAc/hexanes) = 0.37; $[\alpha]_D^{25}$ −135 (*c* 1.85, MeOH); IR (thin film, cm^{-1}) 3408, 2967, 1710, 1647, 1249, 1131, 1073, 733; ^1H NMR (270 MHz, $CDCl_3$): δ 6.90 (qq, *J* = 6.2, 1.0 Hz, 1H), 6.78 (dd, *J* = 9.9, 3.2 Hz, 1H), 6.07 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.39 (ddd, *J* = 7.2, 3.2, 1.5 Hz, 1H), 4.53 (ddd, *J* = 7.4, 7.4, 4.5 Hz, 1H), 3.56 (dq, *J* = 6.2, 6.2 Hz, 1H), 3.33 (dd, *J* = 12.0, 6.2 Hz, 1H), 2.61 (br/s, 1H), 2.47 (br/s, 1H), 1.88 (m, 2H), 1.81 (s, 3H), 1.78 (d, *J* = 6.6 Hz, 3H), 1.65 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$): δ 166.9, 162.4, 144.0, 139.9, 127.6, 122.5, 79.9, 75.2, 71.0, 66.3, 28.2, 28.1, 19.6, 14.7, 12.1; ESI HRMS calcd for $[C_{15}H_{22}O_6+Na]^+$: 321.1314, found: 321.1305.

2.4. 4,5-*epi*,*epi*-Phomopsolide D (19a)

4,5-*epi*,*epi*-Phomopsolide D, a colorless oil: R_f (EtOAc) = 0.41; $[\alpha]_D^{25}$ −281 (*c* 1.30, MeOH); IR (thin film, cm^{-1}) 3419, 2979, 2973, 1712, 1381, 1259, 1065; ^1H NMR (270 MHz, $CDCl_3$): δ 6.99 (dd, *J* = 9.7, 5.9 Hz, 1H), 6.88 (qq, *J* = 7.2, 1.0 Hz, 1H), 6.17 (d, *J* = 9.7 Hz, 1H), 5.22 (dd, *J* = 5.9, 2.5 Hz, 1H), 4.52 (ddd, *J* = 8.7, 4.5, 2.7 Hz, 1H), 3.56 (dq, *J* = 6.4, 6.2 Hz, 1H), 3.33 (m, 1H), 2.65 (br/s, 1H), 2.40 (br/s, 1H), 1.89 (m, 3H), 1.79 (s, 3H), 1.76 (d, *J* = 7.2 Hz, 3H), 1.45 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$): δ 167.0, 163.2, 141.0, 139.8, 127.6, 124.8, 79.6, 75.9, 71.1, 63.2, 29.1, 27.0, 19.7, 14.6, 12.1; ESI HRMS calcd for $[C_{15}H_{22}O_6+Na]^+$: 321.1314, found: 321.1316.

2.5. 5-*epi*-Phomopsolide D (19b)

5-*epi*-Phomopsolide D, a colorless oil: R_f (EtOAc) = 0.50; $[\alpha]_D^{25}$ +102 (*c* 1.60, MeOH); IR (thin film, cm^{-1}) 3408, 2974, 2927, 1713, 1647, 1253, 1133, 1074; ^1H NMR (270 MHz, $CDCl_3$): δ 6.89 (qq, *J* = 6.9, 1.0 Hz, 1H), 6.77 (dd, *J* = 9.9, 3.2 Hz, 1H), 6.06 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.38 (ddd, *J* = 6.9, 3.2, 1.5 Hz, 1H), 4.50 (ddd, *J* = 10.6, 7.4, 3.7 Hz, 1H), 3.55 (dq, *J* = 6.2, 6.2 Hz, 1H), 3.30 (m, 1H), 2.74 (br/s, 1H), 2.52 (br/s, 1H), 1.96 (m, 2H), 1.80 (s, 3H), 1.77 (d, *J* = 6.6 Hz, 3H), 1.70 (m, 1H), 1.47 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$): δ 166.8, 162.3, 143.8, 139.8, 127.5, 122.4, 80.5, 75.6, 70.9, 66.4, 28.7, 28.6, 19.5, 14.5, 12.0; ESI HRMS calcd for $[C_{15}H_{22}O_6+Na]^+$: 321.1314, found: 321.1318.

Acknowledgements

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15. Considerable effort was made to improve the selectivity of the reduction of **13**, however, all these efforts were met with only a diminishment in selectivity. For example, a 1:1 ratio of **14a** and **14b** was obtained when $CeCl_3$ was removed from the reaction conditions.
16. We found a significantly higher optical rotation for **1d** than what was reported from the isolation work, Ref. 2. This is most likely a concentration effect (1.25 mg/mL as opposed to 0.0045 mg/mL).