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Chemoenzymatic synthesis of deoxy analogues of the DNA topoisomerase II inhibitor eleutherin and the 3C-protease inhibitor thysanone

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Abstract

The asymmetric synthesis of (−)-9-demethoxyeleutherin **6**, (+)-9-demethoxyeleutherin **7** and (+)-7,9-deoxythysanone **8** has been achieved using a microwave assisted kinetic resolution of racemic alcohol **11** with Novozyme 435® as the key step.

Keywords: Eleutherin; Thysanone; Topoisomerase II inhibitor; 3C-protease inhibitor; Novozyme 435® (*Candida antarctica* lipase); Microwave assisted lipase kinetic resolution; Intramolecular cyclization

1. Introduction

The pyranonaphthoquinone family of antibiotics is isolated from plants, fungi and aphid pigments and has been shown to exhibit activity against various Gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity.[1] This class of compounds has been postulated to act as bioreductive alkylating agents and hence is important structural leads for cancer therapy.[2] Monomeric members of the pyranonaphthoquinone family that contain a 1,3-disubstitution pattern on the pyran ring include eleutherin **1**, thysanone **2**, isoeleutherin **3**, ventiloquinone E **4** and 6-hydroxy-7-methoxyeleutherin **5** (Fig. 1).

Eleutherin **1** was isolated[3] from the tubers of *Eleutherine bulbosa* (Iridaceae) and was identified as a catalytic inhibitor of topoisomerase II.[4] A number of racemic syntheses of eleutherin **1** have been reported[6–11] and recently, an enantioselective total synthesis of eleutherin **1** was disclosed in which the (*S*)-stereochemistry at C-3 was derived from ethyl (*S*)-lactate. The strategy adopted involved a poor yielding late stage addition of an oxygenated diene to a bromobenzoquinone unit containing a functionalized pyran ring.[12]

Thysanone **2** was isolated from *Thysanophora penicilloides*[5] and is one of few effective inhibitors of human rhinovirus 3C-protease, thus providing a lead compound for development of chemotherapeutic agents for the common cold. We have previously reported the enantioselective synthesis of (+)-7,9-deoxythysanone in which the stereochemistry at C-3 was controlled by using a Sharpless asymmetric

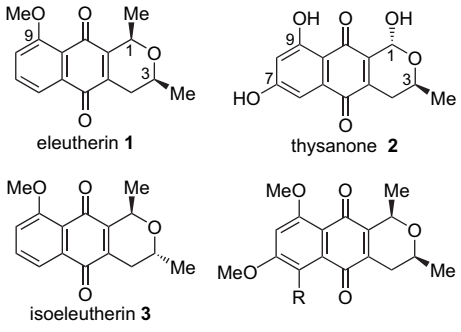

Figure 1. Pyranonaphthoquinone family of antibiotics.

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dihydroxylation of an allylnaphthalene. Its enantiomer was accessible via a chiral oxazaborolidine reduction of methyl ketone.[13] In addition, several lengthy syntheses of analogues of thysanone **2** have been reported[14–16] as well as an asymmetric synthesis confirming the relative stereochemistry of thysanone.[17]

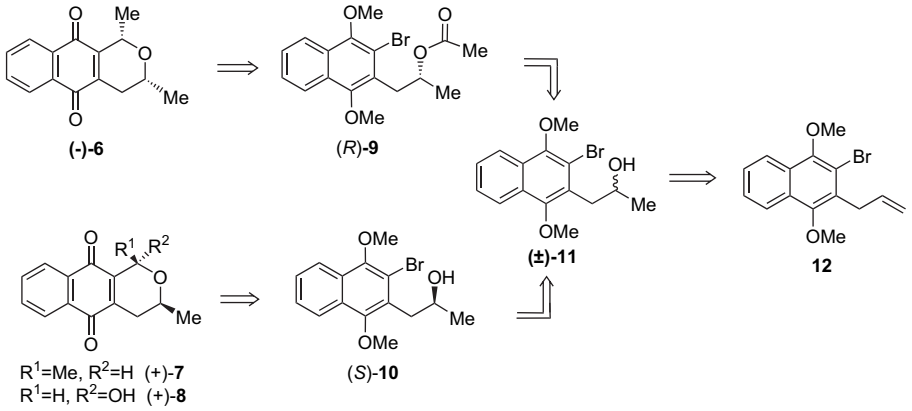
Given the significant biological activity combined with our continuing interest in the synthesis of pyranonaphthoquinone antibiotics,[18] we herein report the efficient asymmetric synthesis of (−)-9-demethoxyetheutherin **6**, (+)-9-demethoxyetheutherin **7** and 7,9-deoxythysanone **8**, whereby the C-3 stereocentre is obtained using a microwave assisted kinetic resolution.

2. Results and discussion

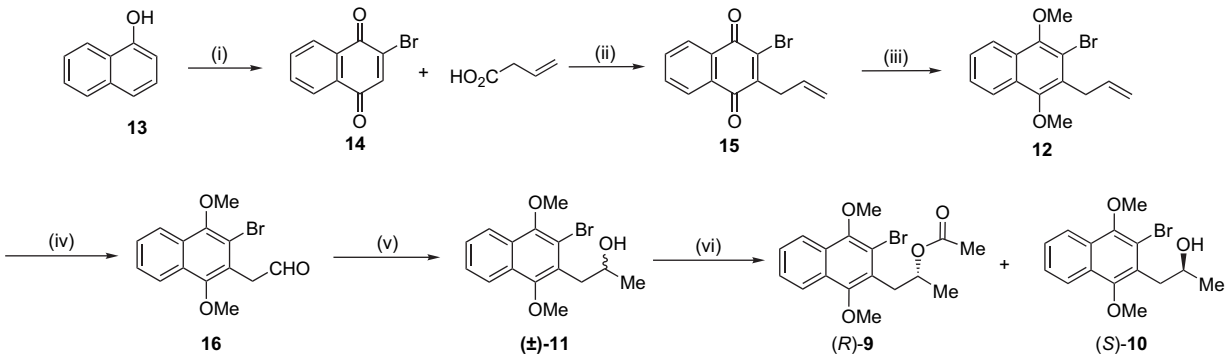
The retrosynthetic analysis adopted is outlined in Scheme 1. It was envisaged that (−)-9-demethoxyeleutherin **6** would be available from (*R*)-bromoacetate **9** in which the stereochemistry at C-3 is introduced by incorporating our recently disclosed microwave assisted lipase kinetic resolution[19] of racemic secondary alcohols. Racemic alcohol **11** can then be accessed from allylbromonaphthalene **12** by oxidative cleavage followed by Grignard addition. Halogen−metal exchange of (*R*)-bromoacetate **9** followed by concomitant intramolecular cyclization of the resulting aryllithium would furnish the pyran ring, delivering (−)-demethoxyeleutherin **6** after oxidative demethylation. Similarly, (+)-9-demethoxyeleutherin **7** could be accessed in the same fashion from (*S*)-alcohol **10**, which is also available from racemic alcohol **11** using the microwave assisted lipase kinetic resolution protocol. Using the same intermediate (*S*)-alcohol **10**, (+)-7,9-deoxythysanone **8** could also be accessed via lithium−halogen exchange followed by trapping of the resulting aryllithium with a formyl equivalent, thus triggering intramolecular cyclization.

It was decided that allylbromonaphthalene **12**, a key intermediate previously used for the synthesis of several pyranonaphthoquinones,[13,20,21] could serve as a suitable starting material for the synthesis of racemic alcohol **11** (Scheme 2). Thus, oxidative bromination of 1-naphthol **13** delivered 2-bromo-1,4-naphthoquinone **14**[22] that underwent radical allylation using a silver persulfate-catalyzed oxidative decarboxylation of vinylacetic acid, furnishing allylnaphthoquinone **15**.[20] Reductive methylation[23] delivered allylnaphthalene **12** that underwent ozone mediated oxidative cleavage[24] of the allyl group affording aldehyde **16**[25] in excellent yield. Finally, Grignard addition of methylmagnesium iodide to aldehyde **16** furnished the desired racemic secondary alcohol **11** in 60% yield.

With alcohol **11** in hand, its microwave assisted lipase kinetic resolution could be considered. Thus, a mixture of alcohol **11**, *p*-chlorophenyl acetate (as the acyl donor) and Novozyme 435® (*Candida antarctica* lipase) in toluene was



Scheme 1. Retrosynthetic analysis of (−)-9-demethoxyeleutherin **6**, (+)-9-demethoxyeleutherin **7** and 7,9-deoxythysanone **8**.



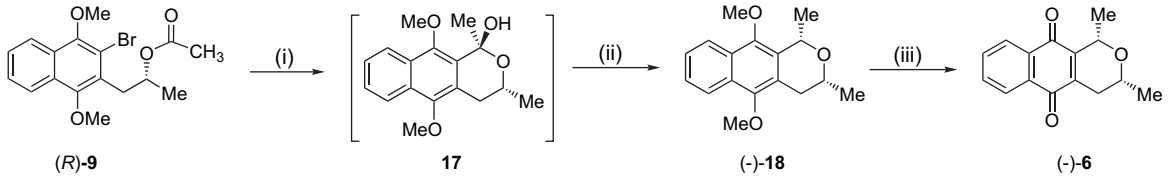
Scheme 2. Reagents and conditions: (i) NBS, AcOH−H_2O, 1 h, 45 °C, 87%; (ii) $AgNO_3$, $(NH_4)_2S_2O_8$, MeCN−H_2O, 2 h, 60 °C, 67%; (iii) $Na_2S_2O_4$, THF, TBAI, aqueous KOH, Me_2SO_4, 4 h, 95%; (iv) O_3, Sudan III®, CH_2Cl_2, 15 min, −60 °C, 72%; (v) MeMgI, Et_2O, 18 h, −78 °C to rt, 60%; (vi) Novozyme 435®, *p*-chlorophenyl acetate, toluene, 60 °C, 70 W, microwave, 6 h, (*S*)-alcohol **10** (40%, 93% ee), (*R*)-ester **9** (45%, 99% ee).

heated to 60 °C in a microwave reactor (CEM Discover system®) at 70 W for 6 h, gratifyingly affording the desired (*R*)-bromoester **9** in 45% yield with 99% ee and (*S*)-alcohol **10**[13] in 40% yield with 93% ee. The enantiomeric excess of both products was established by HPLC using chiralcel OD–H chiral column. The absolute configuration of (*S*)-alcohol **10** obtained was confirmed by comparison of its optical rotation with the value reported in the literature.[13] The assigned (*R*)-configuration of bromoester **9** and (*S*)-configuration of alcohol **10** were also in agreement with Kazlauskas' rule[26] (Scheme 2).

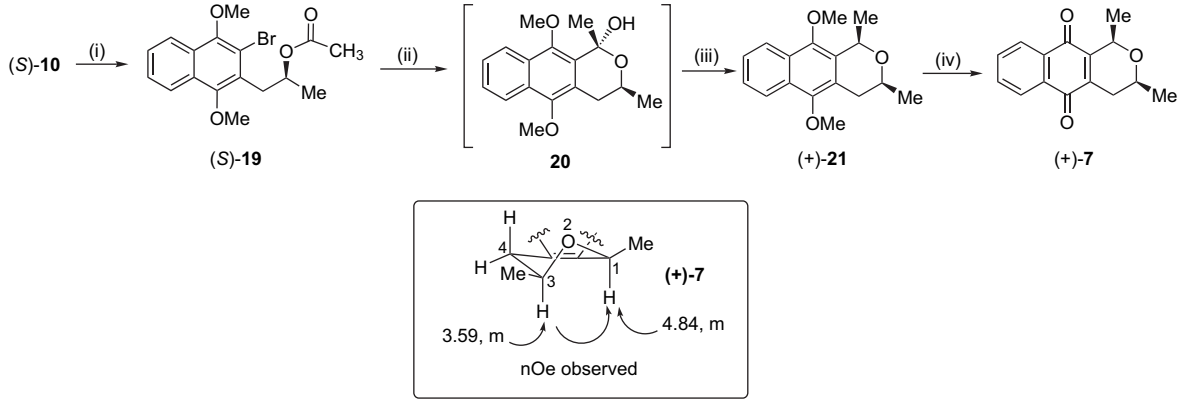
Having established a protocol for the synthesis of enantiopure (*R*)-bromoester **9** and (*S*)-alcohol **10**, their conversion to our desired pyranonaphthoquinone targets was investigated. Initially, (*R*)-bromoester **9** was treated with *tert*-butyllithium at −78 °C to generate the aryllithium triggering concomitant intramolecular cyclization onto the adjacent acetate. Initially, unstable lactol **17** that was formed was immediately converted to the (−)-naphthopyran **18** in 70% yield over two steps using the silane promoted reduction reported by Kraus.[27] The NOESY spectra recorded for (−)-naphthopyran **18** confirmed the cis-stereochemistry between 1-H and 3-H. Finally, CAN-mediated oxidative demethylation gratifyingly delivered (−)-9-demethoxyeleutherin **6** in 75% yield. The enantiomeric excess was calculated by HPLC using a chiralcel AD–H chiral column, and was established to be >99%. The ^{1}H NMR data for (−)-9-demethoxyeleutherin **6** compared well to that reported for the natural eleutherin **1**[3d] and synthetic (+)-eleutherin **1**.[12] The cis-relationship between the two methyl groups at C-1 and C-3 was confirmed by correlation in the NOESY spectra between 1-H and 3-H (Scheme 3).

Given the successful synthesis of (−)-9-demethoxyeleutherin **6** and in order to demonstrate the versatility of this approach, attention next turned to the synthesis of the enantiomer (+)-9-demethoxyeleutherin **7**. Thus, (*S*)-bromoacetate **19** was prepared in excellent yield from (*S*)-alcohol **10** using acetic anhydride in dichloromethane in the presence of a catalytic amount of perchloric acid. In a similar fashion to that described above, lithium–halogen exchange followed by concomitant intramolecular cyclization delivered lactol **20** that upon immediate deoxygenation afforded the stable naphthalene **21**. Finally, oxidative demethylation furnished (+)-9-demethoxyeleutherin **7** in 93% ee (Scheme 4).

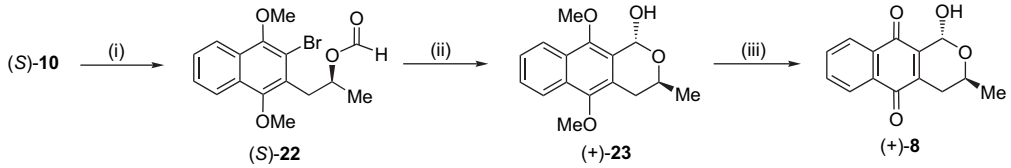
With a view to examine a further use of (*S*)-alcohol **10**, attention next focused on the synthesis of (+)-7,9-deoxythysanone **8**. Following our previously reported procedure,[13] (*S*)-alcohol **10** was treated with *n*-butyllithium and the resulting aryllithium quenched with dimethylformamide. Unfortunately, this procedure did not furnish lactol (−)-**23**, with only debrominated product being isolated from the reaction. This result was attributed to the C-2 position of the (*S*)-alcohol **10** undergoing protonation after lithium–halogen exchange, presumably via internal quenching of the anion by the acidic hydroxyl group proton. In order to circumvent this problem, it was decided to mask the alcohol as its formate, with the hope that lithiation would trigger concomitant intramolecular cyclization in a fashion to that described above. Thus, (*S*)-formate **22** was prepared in excellent yield from (*S*)-alcohol **10** using dicyclohexylcarbodiimide and formic acid in the presence of a catalytic quantity of DMAP. Next, (*S*)-formate **22** gratifyingly underwent cyclization to afford the desired (−)-lactol **23** in 76% yield upon treatment with *tert*-butyllithium.



Scheme 3. Reagents and conditions: (i) *t*-BuLi, THF, 2 h, −78 °C to rt; (ii) Et_3SiH, CF_3CO_2H, CH_2Cl_2, 2 h, −78 °C to rt, 70% (over two steps); (iii) CAN, MeCN–H_2O, 10 min, rt, 75%, 99% ee.



Scheme 4. Reagents and conditions: (i) Ac_2O, CH_2Cl_2, $HClO_4$, 2 h, rt, 94%; (ii) *t*-BuLi, THF, 1 h, −78 °C; (iii) Et_3SiH, CF_3CO_2H, 2 h, rt, 82% (over two steps); (iv) CAN, MeCN–H_2O, 10 min, rt, 72%.



Scheme 5. Reagents and conditions: (i) HCO_2H, DCC, 4-DMAP, CH_2Cl_2, 24 h, 0 °C to rt, 85%; (ii) *t*-BuLi, THF, 1 h, −78 °C, 76%; (iii) CAN, MeCN−H_2O, 10 min, 0 °C, 74%.

Finally, CAN-mediated oxidative demethylation of (−)-lactol **23** provided (+)-7,9-deoxythysanone **8** in 74% yield (Scheme 5). The enantiomeric excess was established to be 95% ee by HPLC using a chiralcel OD−H chiral column. The ^{1}H NMR data for (+)-7,9-deoxythysanone **8** compared well to that reported for natural thysanone **2**[5] and synthetic thysanone **2**.[17] This data clearly established that the lactol ring system in (+)-7,9-deoxythysanone **8** possesses the same relative stereochemistry as both natural and synthetic thysanone **2**.

3. Conclusions

In conclusion, we have developed a concise, simple and flexible enantioselective synthetic route for the preparation of (−)-9-demethoxyeleutherin **6**, (+)-9-demethoxyeleutherin **7** and (+)-7,9-deoxythysanone **8** using a microwave assisted kinetic resolution of racemic alcohol **11** with Novozyme 435® as the key step. Studies directed towards the synthesis of complex pyranonaphthoquinones using this methodology are ongoing.

4. Experimental

4.1. General details

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin−Elmer spectrum One Fourier Transform Infrared spectrometer as a thin film between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin−Elmer 341 polarimeter at λ=598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/TMS solvent, or the residual chloroform peak at δ 7.25 ppm. The ^{13}C NMR values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in hertz) and assignment. Assignments are made with the aide of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV.

4.2. 2-Bromo-1,4-naphthoquinone *14*[22]

To a solution of *N*-bromosuccinimide (14.24 g, 80 mmol) in acetic acid (200 mL) and water (400 mL) at 45 °C was added a solution of 1-naphthol **13** (2.90 g, 20 mmol) in acetic acid (200 mL) dropwise. The mixture was stirred for 1 h at 45 °C then cooled to rt and water (200 mL) was added. The mixture was extracted with chloroform (4×100 mL), the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) solution, water (2×100 mL) and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. The crude product was purified by flash chromatography using hexanes−ethyl acetate (8:2) as eluent to afford the *title compound* **14** (4.17 g, 17.7 mmol, 87%) as a bright yellow solid, mp 132−133 °C (lit.[22] mp 131−132 °C); ν_{max} (film) 1679, 1658, 1590, 1570, 1377, 1246, 1117 cm^{-1}; *m/z* 237 (M[^{81}Br]$^+$, 100), 235 (M[^{79}Br]$^+$, 100), 209 (M[^{81}Br]−O, 40), 207 (M[^{79}Br]−O, 40), 181 (30), 179 (30); HRMS (EI) *m/z* calcd for $C_{10}H_5^{79}BrO_2$, $C_{10}H_5^{81}BrO_2$ (M^+) 235.9473, 237.9452, found 235.9474, 237.9457. The spectroscopic data were in agreement with that reported in the literature.[22]

4.3. 2-Allyl-3-bromo-1,4-naphthoquinone *15*[20]

To a solution of 2-bromo-1,4-naphthoquinone **14** (500 mg, 2.10 mmol) in acetonitrile (50 mL) were added silver nitrate (110 mg, 1.05 mmol) and vinylacetic acid (270 mg, 3.15 mmol) then the mixture was heated to 65 °C. To the reaction mixture was added dropwise a solution of ammonium persulfate (910 mg, 4 mmol) in water (25 mL) over 30 min and stirring continued for 2 h at 65 °C. The mixture was cooled to rt and water (50 mL) was added. The product was extracted with ethyl acetate (3×40 mL), washed with saturated $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography using hexanes−ethyl acetate (96:4) as eluent to afford the *title compound* **15** (389 mg, 1.4 mmol,

67%) as orange/yellow crystals, mp 77–79 °C (lit.[20] mp 79 °C); ν_{max} (film) 1677, 1665, 1596, 1424, 1277, 1265, 738 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_9^{81}BrO_2$, $C_{13}H_9^{79}BrO_2$ (M^+) 277.9765, 275.9786, found 277.9772, 275.9787. The spectroscopic data were in agreement with that reported in the literature.[20]

4.4. 2-Allyl-3-bromo-1,4-dimethoxynaphthalene *12*[20]

To a mixture of 2-allyl-3-bromo-1,4-napthoquinone **15** (340 mg, 1.23 mmol) and tetrabutylammonium iodide (46 mg, 0.11 mmol) in THF (17 mL) under nitrogen was added a solution of sodium dithionite (1.28 g, 7.3 mmol) in water (7 mL) with vigorous stirring. After 30 min, potassium hydroxide (1.58 g, 28.2 mmol) in water (7 mL) was added and the mixture stirred for 1 h followed by the addition of dimethyl sulfate (2.45 mL, 25.2 mmol). The mixture was stirred for 4 h then quenched with aqueous ammonia (8.5 mL, 1.5 M) and water (250 mL). The crude product was extracted with ethyl acetate (3×40 mL). The organic extracts were washed with hydrochloric acid (50 mL, 2 M), water (3×60 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography using hexanes–ethyl acetate (9:1) as eluent to yield the *title compound* **12** (361 mg, 1.2 mmol, 95%) as an off-white solid, mp 56–57 °C (lit.[20] mp 57 °C); ν_{max} (film) 1733, 1577, 1455, 1359, 1265, 1079, 1006 cm^{-1}; MS (EI, %) *m/z* 308 ($M[^{81}Br]^+$, 100), 306 ($M[^{79}Br]^+$, 100), 293 ($M[^{81}Br]$–Me, 40), 291 ($M[^{79}Br]$–Me, 40), 212 (55), 197 (65); HRMS (EI) *m/z* calcd for $C_{15}H_{15}^{81}BrO_2$, $C_{15}H_{15}^{79}BrO_2$ (M^+) 308.0235, 306.0255, found 308.0238, 306.0261. The spectroscopic data were in agreement with that reported in the literature.[20]

4.5. 2-(3-Bromo-1,4-dimethoxynaphthalen-2-yl) ethanol *16*[25]

To a stirred solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene **12** (986 mg, 3.21 mmol) in dichloromethane (120 mL) under nitrogen was added 0.1% solution of Sudan III (three drops) in dichloromethane and the mixture was cooled to −30 °C. Ozone gas was bubbled into the reaction mixture at −60 °C and the reaction mixture turned from pink to pale yellow. Nitrogen gas was flushed into the reaction mixture for 15 min then dimethylsulfide (3.0 mL, 40.80 mmol) was added at −60 °C. The reaction mixture was warmed to rt and stirring was continued for 1 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography (20% ethyl acetate/hexanes) to yield the *title compound* **16** (840 mg, 2.7 mmol, 85%) as a pale pink solid, mp 68–70 °C; R_f (20% ethyl acetate/hexanes) 0.56; ν_{max} (film) 1724, 1579, 1455, 1359, 1265, 1083, 1006 cm^{-1}; δ_H NMR (300 MHz, $CDCl_3$) 9.84 (1H, t, $J_{1,2}$=1.5 Hz, CHO), 8.10–8.01 (2H, m, 5′-H and 8′-H), 7.54–7.49 (2H, m, 6′-H and 7′-H), 4.12 (2H, d, $J_{2,1}$=1.5 Hz, 2-H), 3.95 (3H, s, 1′-OMe), 3.82 (3H, s, 4′-OMe); δ_C (75 MHz, $CDCl_3$) 198.4, 151.7, 150.2, 128.6, 127.5, 127.0, 126.8, 122.8, 122.5, 122.5, 115.7, 62.3, 61.2, 45.0; MS (EI, %) *m/z* 310 ($M[^{81}Br]^+$, 98), 308 ($M[^{79}Br]^+$, 100), 295 ($M[^{81}Br]$–Me, 15), 293 ($M[^{79}Br]$–Me, 15), 200 (55), 185 (76); HRMS (EI) *m/z* calcd for $C_{14}H_{13}^{81}BrO_3$, $C_{14}H_{13}^{79}BrO_3$ (M^+) 310.0028, 308.0048, found 310.0021, 308.0049. The spectroscopic data were in agreement with that reported in the literature.[25]

4.6. 3-Bromo-2-(2-hydroxypropyl)-1,4-dimethoxynaphthalene *11*[13]

A solution of aldehyde **16** (50 mg, 0.16 mmol) in dry diethyl ether (10 mL) was flushed with nitrogen for about 2 min and cooled to −78 °C. An ethereal stock solution of methylmagnesium iodide (0.18 mL, 1.0 M, 0.18 mmol) was added dropwise to the above aldehyde solution. The reaction mixture was allowed to warm to rt overnight. The reaction was quenched with H_2O (10 mL) and stirred for 5 min. The mixture was extracted into ethyl acetate (3×20 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography using hexanes–ethyl acetate (8:2) as eluent to afford the *title compound* **11** (32 mg, 0.01 mmol, 60%) as a white solid, mp 118–120 °C (lit.[13] mp 118–120 °C); ν_{max} (film) 3433, 2103, 1644, 1453, 1358, 1086, 1004 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{17}^{79}BrO_3$, $C_{15}H_{17}^{81}BrO_3$ (M^+) 324.0361, 326.0341, found 324.0360, 326.0347. The spectroscopic data were in agreement with that reported in the literature.[13]

4.7. (*S*)-3-Bromo-2-(2-hydroxypropyl)-1,4-dimethoxynaphthalene *10*[13] and (*R*)-3-bromo-2-(2-acetoxypropyl)-1,4-dimethoxynaphthalene *9*

A mixture of alcohol (±)-**11** (200 mg, 0.6 mmol) and *p*-chlorophenyl acetate (340 mg, 2.0 mmol) in toluene (5 mL) was flushed with argon for 1 min followed by the addition of Novozyme 435® (Sigma–Aldrich) (33 mg). The resulting mixture was stirred at 60 °C in a microwave reactor (single mode CEM Discover® Focused Microwave Synthesis System) at 70 W for 6 h. When the reaction was complete (as indicated by TLC analysis) the mixture was filtered through cotton wool to remove the enzyme and washed with dichloromethane (2×3 mL). The combined organic extracts were concentrated under reduced pressure and the residue purified by flash chromatography using hexanes–ethyl acetate (9:1) as eluent to yield the corresponding alcohol **10** and ester **9**.

The alcohol (*S*)-**10** (80 mg, 0.25 mmol, 40%) was obtained as a white solid, mp 118–120 °C (lit.[13] mp 118–120 °C); $[\alpha]_D^{20}$ +40.8 (*c* 0.001, $CHCl_3$) {lit.[13] $[\alpha]_D$ +8.1 (*c* 2.05, $CHCl_3$)}, 93% ee. The enantiomeric excess (ee) was determined by high performance liquid chromatography (Waters-600) using a chiral column (chiralcel OD–H, 0.43×1 cm, Daicel Chemical Ind. Ltd.) using 2-propanol–hexanes (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the major peak was 32 min and the retention time for the minor peak was 41 min; ν_{max} (film) 3433, 2103, 1644, 1453, 1358, 1086, 1004 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{17}^{79}BrO_3$, $C_{15}H_{17}^{81}BrO_3$ (M^+) 324.0361, 326.0341, found 324.0360,

326.0347. The spectroscopic data were in agreement with that reported in the literature.[13]

Ester (*R*)-**9** (100 mg, 0.27 mmol, 44%) was also obtained as a colourless liquid; $[\alpha]_D^{20}$ +17.8 (*c* 0.17, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high performance liquid chromatography (Waters-600) using a chiral column (chiralcel OD–H, 0.43×1 cm, Daicel Chemical Ind. Ltd.) using 2-propanol–hexanes (0.25:99.75) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 47 min and the retention time for the major peak was 55 min; R_f (10% ethyl acetate/hexanes) 0.41; ν_{max} (film) 2938, 1732, 1567, 1454, 1356, 1239, 1001 cm^{-1}; δ_H NMR (400 MHz, $CDCl_3$) 8.09–8.01 (2H, m, 5-H and 8-H), 7.56–7.49 (2H, m, 6-H and 7-H), 5.46–5.34 (1H, m, 2-H), 3.96 (3H, s, 1-OMe), 3.92 (3H, s, 4-OMe), 3.34 (1H, dd, J_{gem}=13.3 Hz, $J_{1B,2}$=6.2 Hz, 1-H_B), 3.19 (1H, dd, J_{gem}=13.3 Hz, $J_{1A,2}$=6.2 Hz, 1-H_A), 1.94 (3H, s, OCO*Me*), 1.29 (3H, d, $J_{3,2}$=6.3 Hz, 3-H); δ_C (75 MHz, $CDCl_3$) 170.4, 151.6, 150.1, 128.2, 127.6, 126.9, 126.6, 126.6, 122.7, 122.5, 116.7, 70.3, 62.2, 61.3, 36.2, 21.2, 19.7; MS (EI, %) *m/z* 368 (M^+, ^{81}Br, 48), 366 (M^+, ^{79}Br, 48), 308 (100), 306 (100), 293 (27), 291 (30), 281 (15), 279 (20), 212 (50), 200 (45), 185 (50); HRMS (EI) *m/z* calcd for $C_{17}H_{19}^{79}BrO_4$, $C_{17}H_{19}^{81}BrO_4$ (M^+) 366.0467, 368.0446, found 366.0466, 368.0447.

4.8. (S)-3-Bromo-2-(2-acetoxypropyl)-1,4-dimethoxynaphthalene *19*

To a solution of alcohol (*S*)-**10** (81 mg, 0.25 mmol) in dichloromethane (10 mL) was added dropwise acetic anhydride (0.03 mL, 0.29 mmol) with stirring. After 10 min perchloric acid (one drop) was added to the reaction mixture and the resulting violet solution was stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL), extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with saturated NH_4Cl solution (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure and the crude product purified by column chromatography using hexanes–ethyl acetate (9:1) as eluent to yield the *title compound* **19** (86 mg, 0.24 mmol, 94%) as a colourless liquid; $[\alpha]_D^{20}$ −19.2 (*c* 0.03, $CHCl_3$). The ^1H NMR spectrum was identical to that obtained for (+)-(*R*)-acetate **9** as reported above.

4.9. (−)-(1S,3R)-5,10-Dimethoxy-1,3-dimethyl-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran *18*

Bromoester (*R*)-**9** (117 mg, 0.33 mmol) was dissolved in dry THF (5 mL) under nitrogen and the solution cooled to −78 °C. A solution of *tert*-butyllithium in pentane (0.48 mL, 1.6 M, 0.69 mmol) was added dropwise to the above solution until the reaction mixture turned to a pale red colour and the reaction was stirred for 1 h. The reaction was quenched at −78 °C with H_2O (10 mL) followed by gradual warming to rt then extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude lactol **17** (100 mg) which was not purified due to its ready decomposition upon exposure to silica gel.

To a solution of the crude lactol **17** (100 mg) in dry dichloromethane (10 mL) at −78 °C was added trifluoroacetic acid (0.07 mL, 0.96 mmol) dropwise and the mixture stirred for 15 min. Triethylsilane (0.15 mL, 0.96 mmol) was then added dropwise at −78 °C and the mixture stirred for 2 h then allowed to warm to rt over 1 h. The reaction mixture turned to a pale yellow colour and was quenched with ice-water (10 mL) then extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by column chromatography (10% ethyl acetate/hexanes) to afford the *title compound* **18** (60 mg, 0.22 mmol, 70%) as a colourless liquid; R_f (10% ethyl acetate/hexanes) 0.65; $[\alpha]_D^{20}$ −137.5 (*c* 0.02, $CHCl_3$); ν_{max} (film) 2934, 2400, 1449, 1359, 1350, 1215, 1012 cm^{-1}; δ_H NMR (400 MHz, $CDCl_3$) 8.08–8.02 (2H, m, 6-H and 9-H), 7.50–7.44 (2H, m, 7-H and 8-H), 5.24 (1H, q, $J_{1,Me}$=6.3 Hz, 1-H), 3.91 (3H, s, 5-OMe), 3.86 (3H, s, 10-OMe), 3.74–3.68 (1H, m, 3-H), 3.09 (1H, dd, J_{gem}=16.0 Hz, $J_{4eq,3}$=2.0 Hz, 4-H_{eq}), 2.63 (1H, dd, J_{gem}=16.2 Hz, $J_{4ax,3}$=11.0 Hz, 4-H_{ax}), 1.70 (3H, d, $J_{Me,1}$=6.3 Hz, 1-Me), 1.43 (3H, d, $J_{Me,3}$=6.1 Hz, 3-Me); δ_C (100 MHz, $CDCl_3$) 148.8, 148.4, 129.1, 127.4, 127.4, 125.7, 125.5, 125.2, 122.9, 121.1, 71.2, 69.6, 61.2, 60.9, 31.9, 22.4, 21.8; MS (EI, %) *m/z* 272 (M^+, 80), 257 (100), 242 (35), 227 (25), 213 (30), 198 (13), 181 (10), 152 (10), 115 (9), 77 (6); HRMS (EI) *m/z* calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412, found 272.1406.

4.10. (+)-(1R,3S)-5,10-Dimethoxy-1,3-dimethyl-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran *21*

Compound **21** (52 mg, 0.19 mmol, 82%) was obtained from (*S*)-**19** (86 mg, 0.23 mmol) using the same procedure for the preparation of (−)-**18** from (*R*)-**9**; colourless liquid, mp 74–76 °C; $[\alpha]_D^{20}$ +94.5 (*c* 0.11, $CHCl_3$). The spectroscopic data were identical to the (−)-naphthopyran **18**.

4.11. (−)-(1S,3R)-1,3-Dimethyl-3,4-dihydro-1H-naphtho-[2,3-c]pyran-5,10-dione *6*

4.11.1. [(−)-9-Demethoxyeleutherin]

To the stirred solution of naphthopyran (−)-**18** (30 mg, 0.11 mmol) in acetonitrile (10 mL), was added dropwise a solution of ceric ammonium nitrate (149 mg, 0.27 mmol) in water (4 mL) at rt. The reaction mixture was poured into ice-water (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (10% ethyl acetate/hexanes) to afford the *title compound* **6** (20 mg, 0.08 mmol, 75%) as a yellow needles, mp 122–124 °C (lit.[9] mp 122–125 °C); $[\alpha]_D^{20}$ −256.5 (*c* 0.11, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high performance liquid chromatography

(Waters-600) using a chiral column (chiralcel AD–H, 0.43×1 cm, Daicel Chemical Ind. Ltd.), with 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 21 min and the retention time for the major peak was 24 min; R_f (10% ethyl acetate/hexanes) 0.60; ν_{max} (film) 2935, 1660, 1623, 1595, 1295, 1215, 1055 cm^{-1}; δ_H NMR (400 MHz, $CDCl_3$) 8.08–8.00 (2H, m, 6-H and 9-H), 7.67–7.73 (2H, m, 7-H and 8-H), 4.87–4.81 (1H, m, 1-H), 3.63–3.55 (1H, m, 3-H), 2.77 (1H, dt, J_{gem}=18.2 Hz, $J_{4eq,3}$=2.6 Hz, 4-H_{eq}), 2.25 (1H, ddd, J_{gem}=18.6 Hz, $J_{4ax,3}$=10.2 Hz, $J_{4ax,1}$=3.9 Hz, 4-H_{ax}), 1.54 (3H, d, $J_{Me,1}$=6.4 Hz, 1-Me), 1.36 (3H, d, $J_{Me,3}$=6.4 Hz, 3-Me); δ_C (100 MHz, $CDCl_3$) 184.0, 183.9, 146.8, 142.6, 133.7, 133.5, 132.4, 131.8, 126.19, 126.18, 70.0, 68.7, 30.4, 21.2, 20.8; MS (EI, %) *m/z* 242 (M^+, 100), 227 (45), 224 (10), 213 (25), 209 (20), 198 (30), 181 (20), 152 (10), 115 (20), 76 (25); HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_3$ (M^+) 242.0943, found 242.0943. This spectroscopic data were in agreement with racemic compound that reported in the literature.[9]

4.12. (+)-(1R,3S)-1,3-Dimethyl-3,4-dihydro-1H-naphtho-[2,3-c]pyran-5,10-dione **7**

4.12.1. [(+)-9-Demethoxyeleutherin]

Compound **7** (14 mg, 0.06 mmol, 72%) was obtained from (+)-**21** using the same procedure for the preparation of **6** from (−)-**18**; yellow needles, mp 122–124 °C (lit.[9] mp 122–125 °C); $[\alpha]_D^{20}$ +227.2 (*c* 0.10, $CHCl_3$), 93% ee. The enantiomeric excess (ee) was determined by high performance liquid chromatography (Waters-600) using a chiral column (chiralcel AD–H, 0.43×1 cm, Daicel Chemical Ind. Ltd.) using 2-propanol–hexanes (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the major peak was 21 min and the retention time for the minor peak was 24 min. The ^1H NMR spectrum was identical to the (−)-9-demethoxyeleutherin **6** reported above.

4.13. (S)-3-Bromo-2-(2-formylpropyl)-1,4-dimethoxy-naphthalene **22**

To a solution of bromoalcohol (*S*)-**10** (50 mg, 0.15 mmol) in dry dichloromethane (5 mL) was added formic acid (45 mg, 0.32 mmol). The reaction mixture was cooled to 0 °C under nitrogen, 4-dimethylaminopyridine (2 mg) was added and the reaction mixture stirred for 2 min followed by the addition of dicyclohexylcarbodiimide (40 mg, 0.195 mmol). After 15 min, the mixture was warmed to rt and stirred for 24 h. The resulting precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The crude residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford the *title compound* **22** (46 mg, 0.13 mmol, 85%) as a colourless liquid; R_f (10% ethyl acetate/hexanes) 0.50; $[\alpha]_D^{20}$ −25.4 (*c* 0.19, $CHCl_3$); ν_{max} (film) 2936, 2400, 1719, 1570, 1455, 1360, 1215 cm^{-1}; δ_H NMR (300 MHz, $CDCl_3$) 8.18–8.00 (2H, m, 5-H and 8-H), 7.95 (1H, s, OC*H*O), 7.60–7.50 (2H, m, 6-H and 7-H), 5.57–5.47 (1H, m, 2-H), 3.96 (3H, s, 1-OMe), 3.93 (3H, s, 4-OMe), 3.41 (1H, dd, J_{gem}=13.4 Hz, $J_{1B,2}$=6.1 Hz, 1-H_B), 3.21 (1H, dd, J_{gem}=13.4 Hz, $J_{1A,2}$=6.1 Hz, 1-H_A), 1.35 (3H, d, $J_{3,2}$=6.3 Hz, 3-H); δ_C (75 MHz, $CDCl_3$) 160.5, 151.7, 150.2, 128.2, 127.6, 126.7, 126.6, 126.4, 122.8, 122.6, 116.4, 70.4, 62.3, 61.3, 36.2, 19.8; MS (EI, %) *m/z* 354 (M^+, ^{81}Br, 100), 352 (M^+, ^{79}Br, 100), 308 (75), 306 (75), 293 (25), 291 (25), 267 (20), 265 (20), 230 (45), 212 (70), 200 (50), 185 (65), 171 (20), 127 (20), 115 (20); HRMS (EI) *m/z* calcd for $C_{16}H_{17}^{81}BrO_4$, $C_{16}H_{17}^{79}BrO_4$ (M^+) 354.0290, 352.0310, found 354.0298, 352.0314.

4.14. (−)-(1R,3S)-9,10-Dimethoxy-1-hydroxy-3-methyl-3,4-dihydro-1H-naphtho[2,3-c]pyran **23**[13]

Formate (*S*)-**22** (46 mg, 0.13 mmol) was dissolved in dry THF (7 mL) under nitrogen and the solution cooled to −78 °C. *tert*-Butyllithium in pentane (0.17 mL, 1.6 M, 0.27 mmol) was added dropwise to the above solution. The colourless reaction mixture turned to dark red and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with H_2O (5 mL) at −78 °C then left to warm to rt. The crude mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue that was purified by flash chromatography using hexanes–ethyl acetate (7:3) as eluent to afford the *title compound* **23** (27 mg, 0.01 mmol, 76%) as colourless crystals, mp 145–146 °C (lit.[13] mp 146–147 °C); $[\alpha]_D^{20}$ −39.2 (*c* 1.19, $CHCl_3$); HRMS (EI) *m/z* calcd for $C_{16}H_{18}O_4$ (M^+) 274.1205, found 274.1202. The spectroscopic data were in agreement with that reported in the literature.[13]

4.15. (+)-(1R,3S)-1-Hydroxy-3-methyl-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran-5,10-dione **8**

4.15.1. [(+)-7,9-Deoxythysanone][13]

A stirred solution of lactol (−)-**23** (11.5 mg, 0.04 mmol) in acetonitrile (5 mL) was cooled to 0 °C and a solution of ceric ammonium nitrate (46 mg, 0.08 mmol) in water (5 mL) was added dropwise. The reaction mixture was warmed to rt then poured into water (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by column chromatography using hexanes–ethyl acetate (7:3) as eluent to afford the *title compound* **8** (7.5 mg, 0.03 mmol, 74%) as a pale yellow solid, mp 161–162 °C (lit.[13] mp 161–162 °C); $[\alpha]_D^{20}$ +139.3 (*c* 0.76, CH_2Cl_2) {lit.[9] $[\alpha]_D$ +29.5 (*c* 0.80, CH_2Cl_2)}, 95% ee. The enantiomeric excess (ee) was determined by high performance liquid chromatography (Waters-600) using a chiral column (chiralcel OD–H, 0.43×1 cm, Daicel chemical Ind. Ltd.) using 2-propanol–hexanes (1:99) as eluent, and a flow rate of 0.5 mL/min. The retention time for the major peak was 77 min and the retention time for the minor peak was 97 min; MS (EI, %) *m/z* 244 (M^+, 20), 243 (25), 226 (50), 200 (100), 172 (60), 115 (50), 105 (20), 76 (28); HRMS (EI) *m/z* calcd for $C_{14}H_{12}O_4$ (M^+)

244.0736, found 244.0729. The spectroscopic data were in agreement with that reported in the literature.[13]

References and notes

1. (a) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic: London, 1971; p 282; See also p 597; (b) For a review on the isolation and structure of pyranonaphthoquinone antibiotics, see: Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267.
2. Moore, H. W. *Science* **1977**, *197*, 527.
3. (a) Schmid, H.; Meijer, T. M.; Ebnother, A. *Helv. Chim. Acta* **1950**, *33*, 595; (b) Schmid, H.; Ebnother, A.; Meijer, T. M. *Helv. Chim. Acta* **1950**, *33*, 1751; (c) Schmid, H.; Ebnother, A. *Helv. Chim. Acta* **1951**, *34*, 561; (d) Cameron, D. W.; Kingston, D. G. I.; Sheppard, N.; Todd, A. R. *J. Chem. Soc.* **1964**, 98.
4. (a) Krishnan, P.; Bastow, K. F. *Biochem. Phramacol.* **2000**, *60*, 1367; (b) Hara, H.; Maruyama, N.; Yamashita, S.; Hayashi, Y.; Lee, K.-H.; Bastow, K. F.; Chairul, R. M.; Imakura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1714.
5. Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A. *Tetrahedron Lett.* **1991**, *32*, 5279.
6. Kobayashi, K.; Uchida, M.; Uneda, T.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **1998**, *39*, 7725.
7. Uno, H. *J. Org. Chem.* **1986**, *51*, 350.
8. Naruta, Y.; Uno, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1277.
9. Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191.
10. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.
11. Giles, G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; York, S. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2383.
12. Tewierik, L. M.; Dimitriadis, C.; Donner, C. D.; Gill, M.; Willems, B. *Org. Biomol. Chem.* **2006**, *4*, 3311.
13. Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **2002**, *58*, 183.
14. Brimble, M. A.; Houghton, S. I.; Woodgate, P. D. *Tetrahedron* **2007**, *63*, 880.
15. Bulbule, V. J.; Priti, P. S.; Deshpande, V. H.; Hanumant, B. *Tetrahedron* **2007**, *63*, 166.
16. Kraus, A. G.; Ogutu, H. *Tetrahedron* **2002**, *58*, 7391.
17. Donner, C. D.; Gill, M. *Tetrahedron Lett.* **1999**, *40*, 3921; Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938.
18. (a) Brimble, M. A.; Nairn, M. R.; Park, J. S. O. *Org. Lett.* **1999**, *1*, 1459; Brimble, M. A.; Nairn, M. R.; Park, J. S. O. *J. Chem. Soc., Perkin Trans. 1* **2000**, 697; (b) Brimble, M. A.; Brenstrum, T. J. *Tetrahedron Lett.* **2000**, *41*, 2991; Brimble, M. A.; Brenstrum, T. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1624; (c) Brimble, M. A.; Davey, R. M.; McLeod, M. D. *Synlett* **2002**, 1318; Brimble, M. A.; Davey, R. M.; McLeod, M. D.; Murphy, M. *Org. Biomol. Chem.* **2003**, *1*, 1690; (d) Brimble, M. A.; Neville, D.; Duncalf, L. J. *Tetrahedron Lett.* **1998**, *39*, 5647; Brimble, M. A.; Duncalf, L. J.; Neville, D. *J. Chem. Soc., Prekin Trans. 1* **1998**, 4165; (e) Brimble, M. A.; McEwan, J. F.; Turner, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1257; (f) Brimble, M. A.; Lai, M. Y. H. *Org. Biomol. Chem.* **2003**, *1*, 4227; (g) Brimble, M. A.; Laita, O.; Robinson, J. E. *Tetrahedron* **2006**, *62*, 3021.
19. Bachu, P.; Gibson, J. S.; Sperry, J.; Brimble, M. A. *Tetrahedron: Asymmetry* **2007**, *13*, 1618.
20. Kesteleyn, B.; De Kimpe, N.; Puyvelde, L. V. *J. Org. Chem.* **1999**, *64*, 1173.
21. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4725.
22. Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305.
23. Kraus, G. A.; Man, T. O. *Synth. Commun.* **1986**, *16*, 1037.
24. Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
25. Brimble, M. A.; Bachu, P.; Sperry, J. *Synthesis* **2007**, 2887.
26. Kazlauskas, R. J.; Weissfloch, A. N.; Rapaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
27. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273.