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# Chiral vicinal diols as platforms for separable diastereomers in Johnson–Claisen rearrangement: a new short route to (−)-nor-canadensolide, (−)-canadensolide and (−)-sporothriolide

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ABSTRACT

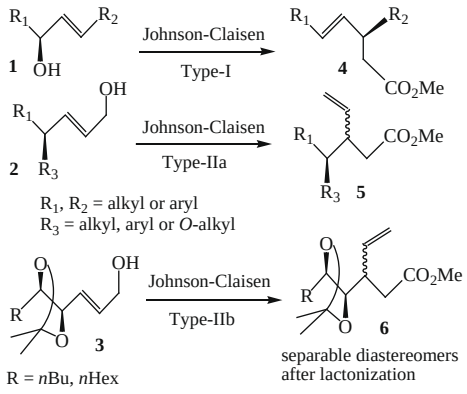
The chiral vicinal diols prepared by asymmetric dihydroxylation in high enantioselectivities provide an excellent platform for separable diastereomers in the Johnson–Claisen rearrangement. The separated *syn*-diastereomers were converted into the advanced γ-(lactone-lactol) intermediates (in six steps, 26–27% overall yields) for the synthesis of (−)-nor-canadensolide, (−)-canadensolide and (−)-sporothriolide.



The Johnson–Claisen rearrangement ([3,3] sigmatropic)[1a] of substrates having a chiral secondary allyl alcohol, for example, **1** is known for 1,3-chirality transfer[1b–e] in the reactions of type-I, giving **4** (Scheme 1), while in most cases for primary allyl alcohols of type-II, for example, **2**[2] or **3**, a mixture of diastereomers **5** or **6**, respectively, is obtained. However, when the two diastereomers are separable (Type-IIb, **6**), it offers an opportunity for further elaboration to target the synthesis of natural products. Herein, we have exploited this possibility in the synthesis of γ-(lactone-lactol) intermediates for (−)-nor-canadensolide **7**, (−)-canadensolide **8** and (−)-sporothriolide **9** (Fig. 1). The substrates for the Johnson-Claisen rearrangement (Type-IIb, **3**, Scheme 1) are based on chiral vicinal diols which can be synthesized in high enantioselectivity by asymmetric dihydroxylation.[3]

Canadensolide[4] **8**, a fungicidal agent and sporothriolide[5] **9**, an antibacterial, antifungal, algicidal and herbicidal agent isolated from the fungus *Penicillium canadense* and *Sporothrix* sp. (Strain No. 700), respectively, are closely related bis-γ-lactones which differ only in the chain length of the alkyl group (Fig. 1). These have been the targets of considerable synthetic interest.[6] In most syntheses of canadensolide **8**, the γ-(lactone–lactol) structure **10** (Scheme 2) is built through various methods. The exocyclic methylene group is introduced at the last stage[6e,i,j] and this method is cited by many authors,[6l,n,q–s] leading to the formal syntheses of **8**.

As part of our research programme aimed at the enantioselective synthesis of bioactive natural products,[7] we designed a new short route based on chiral vicinal diols as excellent platforms for the synthesis of separable diastereomers in the Johnson–Claisen rearrangement for the advanced intermediates towards the synthesis of nor-canadensolide, canadensolide and sporothriolide. The synthesis of the γ-(lactone–lactol) **10** can be visualized from com-




R = *n*Bu, *n*Hex

**Scheme 1.** Chirality transfer in the Johnson–Claisen rearrangement.

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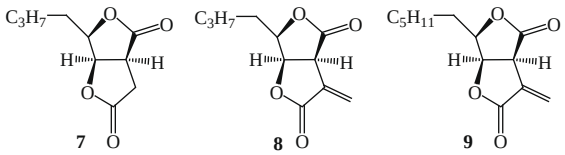
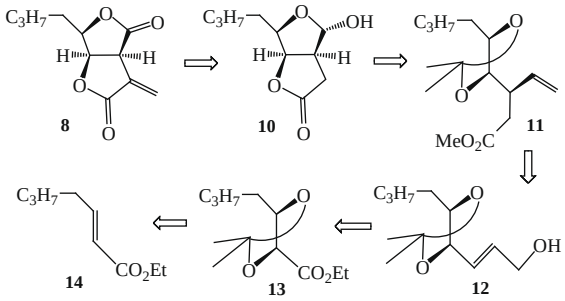
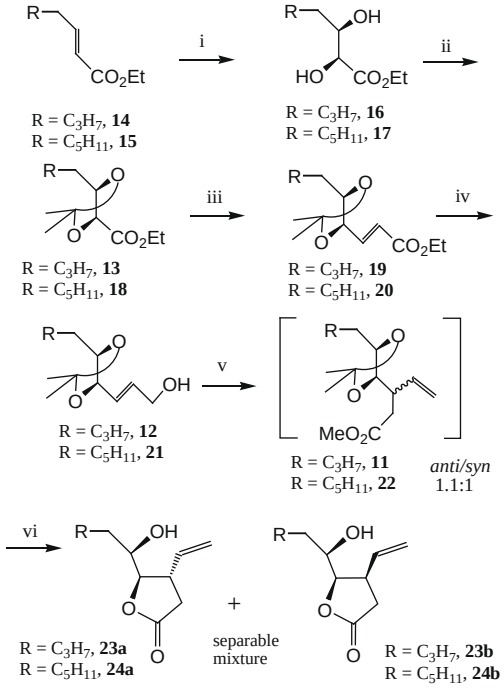


**Figure 1.** (−)-Nor-canadensolide **7**, (−)-Canadensolide **8** and (−)-sporothriolide **9**.



**Scheme 2.** Retrosynthetic analysis of canadensolide **8**.

pound **11** (Scheme 2) through lactonization and cleavage of the terminal double bond. Compound **11** can be obtained through the Johnson–Claisen rearrangement of allyl alcohol **12** (Type-IIb, Scheme 1). The allyl alcohol **12** can easily be derived from **13**.

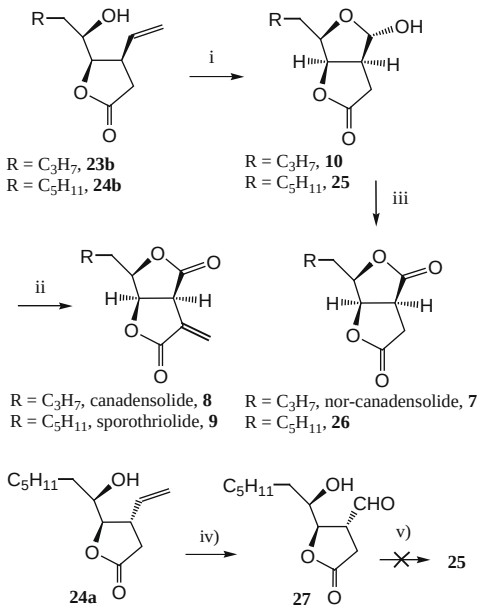


**Scheme 3.** Synthesis of separable diastereomers **23a/23b** and **24a/24b** through the Johnson–Claisen rearrangement. Reagents and conditions: (i) $K_3Fe(CN)_6$ (3.0 equiv), $K_2CO_3$ (3.0 equiv), $(DHQD)_2$-PHAL (1.0 mol %), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH/$H_2O$ (1:1), 0 °C, 24 h, 96%, 99%ee for each (**16** and **17**); (ii) $Me_2C(OMe)_2$ (3.0 equiv), $Me_2CO$, *p*-TsOH (cat), rt, 12 h, 98% for each (**13** and **18**); (iii) (a) DIBAL-H (1.0 equiv), $CH_2Cl_2$, −78 °C, 2 h; (b) $Ph_3P{=}CHCO_2Et$ (1.2 equiv), THF, rt, 12 h, 91% for both **19** and **20** (from **13** and **18**, respectively); (iv) DIBAL-H (2.3 equiv), $CH_2Cl_2$, 0 °C, 2 h, rt, 2 h, 97% for each (**12** and **21**); (v) $(MeO)_3CMe$, xylene, $EtCO_2H$ (cat), reflux, 4 h; (vi) 4 N HCl, MeOH, rt, 12 h, **23a** (46%), **23b** (42%) from **12** (based on 26% recovered **12**); **24a** (47%), **24b** (42%) from **21** (based on 27% recovered **21**).

The enantiopure **13** can be obtained through the Sharpless asymmetric dihydroxylation[3] of olefin **14** and acetonide protection.

The synthesis of the precursor **23b** and **24b** for γ-(lactone–lactol) intermediates **10** and **25**, respectively, is shown in Schemes 3 and 4. The Sharpless asymmetric dihydroxylation of olefin **14**[8] gave the diol **16** in high yield of 96% and excellent enantioselectivity of 99% ee[9] (Scheme 3). Similarly, the olefin **15**[10] provided the diol **17** (96%, 99% ee[9]). The diol protection of **16** and **17** afforded the corresponding acetonides **13** and **18**, each in 98% yield. The subsequent DIBAL-H reduction of the ester group in **13** and the Wittig olefination of the corresponding aldehyde gave the α,β-unsaturated ester **19** in 91% yield. Similarly, **18** provided **20** in 91% yield. Further, the DIBAL-H reduction of the esters **19** and **20** provided the allyl alcohols **12** and **21**, respectively, each in 97% yield. The Johnson–Claisen rearrangement of **12**, with trimethylorthoacetate and catalytic propionic acid over 14 h in refluxing toluene solvent, provided the diastereomeric mixture of **11**, *anti*/*syn* in 3:1 ratio.[11a] However, the same reaction when carried out for a period of 4 h in refluxing xylene gave the diastereomeric mixture of **11**, *anti*/*syn* in calcd 1.1:1 ratio.[11] The mixture was treated with 4 N HCl in MeOH, which then hydrolyzed the acetonide, and concomitant lactonization provided the column chromatographically separable mixture of lactones **23a** and **23b**[12,13] in 46% and 42% yields, respectively, based on 26% recovered starting material **12** before lactonization.[14] In a similar sequence of reactions, the allyl alcohol **21** after the Johnson–Claisen rearrangement provided the diastereomeric mixture **22**, *anti*/*syn* in calcd 1.1:1 ratio[11] and further hydrolysis provided the separable mixture of lactones **24a** and **24b** in 47% and 42% yields, respectively, based on 27% recovered starting material **21** before lactonization.

The lactone **23b** was subjected to ozonolytic cleavage (Scheme 4) of the terminal double bond, and subsequent $Ph_3P$ work-up afforded the γ-(lactone-lactol) intermediate **10**[6i,6s,15] in a good yield of 96%, $[\alpha]_D^{25}$ −13.5 (*c* 2, $CHCl_3$), lit.[6s] −10.0 (*c* 0.2, $CHCl_3$). The synthesis of canadensolide **8** from **10** involves the introduction of an exocyclic methylene group and is known in the literature.[6e,i,j]



**Scheme 4.** Synthesis of γ-(lactone–lactol) intermediates **10**, **25** and nor-canadensolide **7**. Reagents and conditions: (i) $O_3$, $CH_2Cl_2$, −78 °C, 0.5 h, then $Ph_3P$ (1.2 equiv), −78 °C, 1 h, rt, 1 h, 96% for each (**10** and **25**); (ii) Ref. 6e,i,j; (iii) PCC (4.0 equiv), $CH_2Cl_2$, rt, 6 h, 81% for each (**7** and **26** from **23b** and **24b**, respectively); (iv) $O_3$, $CH_2Cl_2$, −78 °C, 0.5 h, then $Ph_3P$ (1.2 equiv), −78 °C, 1 h, rt, 1 h, 95%; (v) See Ref. 18.

After ozonolysis of **23b** and $Ph_3P$ work-up, the crude compound **10** was in situ oxidized with PCC to afford the bis-γ-lactone **7**, also known as nor-canadensolide,[6i,6s,15] in 81% yield. On the other hand, the ozonolysis of **24b** and subsequent $Ph_3P$ work-up afforded the γ-(lactone–lactol) intermediate **25**[16] in 96% yield (Scheme 4). When the crude lactol **25** was in situ oxidized with PCC, the bis-γ-lactone **26** (81%) was obtained similar to nor-canadensolide **7**. The *anti*-lactone **24a** was subjected to ozonolysis to give the corresponding aldehyde **27**[17] in 95% yield, which did not cyclize. This further confirms the *anti* geometry in **24a** (similarly in **23a**). All attempts to epimerize the α-carbon centre of aldehyde **27** failed to deliver **25**.[18] It either decomposed or gave a multi-component mixture. The γ-(lactone–lactol) intermediate **25** matched exactly onto the advanced intermediate **10** (in the synthesis of canadensolide), and we believe[6r] that this (**25**) can lead to the total synthesis of sporothriolide **9** in a similar sequence of reactions involving introduction of the exocyclic methylene group.[6e,i,j]

In summary, we have developed a short route to the highly enantio- and diastereoselective syntheses of (−)-nor-canadensolide and advanced γ-(lactone–lactol) intermediates for (−)-canadensolide and (−)-sporothriolide based on chiral vicinal diols (prepared in high enantioselectivity by asymmetric dihydroxylation) which act as good platforms for separable diastereomers in the Johnson–Claisen rearrangement. This strategy represents the shortest route (six steps, 26–27% overall yields) to the intermediates **10** and **25**. A further improvement in the *syn*-diastereoselectivity in the Johnson–Claisen rearrangement and application of this strategy in the synthesis of other related natural products is in progress.

## Acknowledgements

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9. Enantiomeric excess was determined by chiral HPLC. Column: Chiralpak IA No. IA00CE-KL063, eluent: *n*-hexane/*i*-PrOH (95:5), flow rate: 0.5 mL/min, UV detector: 240 nm.
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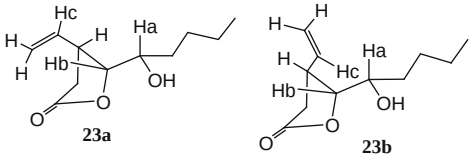
11. (a) Diastereomeric ratio was determined by $^1$H NMR of the mixture. Here, the *anti*/*syn* refers to the C4/C5 relative configuration of protons.; (b) The reaction was not continued over 4 h to avoid higher amounts of *anti*-diastereomer. When the reaction was carried out over a shorter period, lower yields were obtained with no change in the *anti*/*syn* ratio.
12. The relative configuration of **23a** and **23b** is based on the comparison of the chemical shifts of Ha and Hb protons in the lactones. In **23a**, the Hb proton is syn to the vinyl group and is shielded to $\delta$ 4.12 as compared to Hb ($\delta$ 4.38) in **23b.**




13. The *syn*-geometry in **23b** is further confirmed after the ozonolysis reaction by the fact that it cyclizes to give the γ-(lactone–lactol) intermediate **10** (Scheme 4).
14. *Data for* **23a**: Colourless oil. $[\alpha]_D^{25}$ −48.4 (*c* 1.9, $CHCl_3$). IR ($CHCl_3$): $\nu$ = 3414, 1774, 1525, 1419 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 0.91 (t, *J* = 6.8 Hz, 3H), 1.19–1.64 (m, 6H), 2.15 (br s, 1H, OH), 2.50 (dd, *J* = 17.9, 9.6 Hz, 1H), 2.79 (dd, *J* = 17.6, 8.9 Hz, 1H), 3.27 (quint, *J* = 8.7 Hz, 1H), 3.60–3.63 (m, 1H), 4.12 (dd, *J* = 7.8, 2.2 Hz, 1H), 5.19 (d, *J* = 11 Hz, 1H), 5.23 (d, *J* = 18.3 Hz, 1H), 5.78 (ddd, *J* = 18.3, 11, 8.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$/$CHCl_3$): $\delta$ = 13.84, 22.39, 27.68, 33.73, 35.16, 41.16, 70.62, 86.45, 117.95, 136.12, 176.16. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+H] calcd for $C_{11}H_{19}O_3$: 199.1334, found 199.1341. *Data for* **23b**: Colourless oil. $[\alpha]_D^{25}$ −50.3 (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): $\nu$ = 3420, 1790, 1613, 1523, 1418 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 0.91 (t, *J* = 6.8 Hz, 3H), 1.2–1.71 (m, 7H, OH), 2.6 (dd, *J* = 17.4, 9.1 Hz, 1H), 2.72 (dd, *J* = 17.4, 9.1 Hz, 1H), 3.3 (quint, *J* = 8.2 Hz, 1H), 3.74–3.76 (m, 1H), 4.38 (dd, *J* = 8, 2.9 Hz, 1H), 5.22 (d, *J* = 11 Hz, 1H), 5.24 (d, *J* = 5.1 Hz, 1H), 5.97 (ddd, *J* = 11, 8.2, 5.1 Hz, 1H). $^{13}$C NMR (100 , $CDCl_3$/$CHCl_3$): $\delta$ = 13.90, 22.45, 27.61, 32.98, 34.73, 42.76, 71.02, 84.30, 118.72, 134.64, 176.80. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+H] calcd for $C_{11}H_{19}O_3$: 199.1334, found 199.1339.
15. The spectroscopic and analytical data were in full agreement with those reported.[6i,s]
16. *Data for* **25**: Colourless oil. $[\alpha]_D^{25}$ −71.9 (*c* 1, $CHCl_3$). IR ($CHCl_3$): $\nu$ 3396, 1774, 1523, 1421 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.29–1.43 (m, 8H), 1.67–1.74 (m, 2H), 2.50 (dd, *J* = 18.5, 3.6 Hz, 1H), 2.85 (dd, *J* = 18.5, 11.2 Hz, 1H), 3.07 (td, *J* = 11.2, 3.6 Hz, 1H), 3.25 (br s, OH), 4.24 (td, *J* = 6.8, 3.6 Hz, 1H), 5.0 (dd, *J* = 6.8, 3.6 Hz, 1H), 5.32 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$/$CHCl_3$): $\delta$ = 13.99, 22.50, 25.96, 28.39, 29.18, 31.61, 32.02, 46.17, 79.18, 83.66, 102.89, 176.25. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+Na] calcd for $C_{12}H_{20}O_4Na$: 251.1259, found 251.1257.
17. *Data for* **27**: Colourless oil. $[\alpha]_D^{25}$ −25 (*c* 1, $CHCl_3$). IR ($CHCl_3$): $\nu$ = 3436, 2860, 1760, 1726, 1462 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 0.89 (t, *J* = 7.0 Hz, 3H), 1.22–1.51 (m, 8H), 1.63 (t, *J* = 7.1 Hz, 2H), 2.90 (d, *J* = 8.2 Hz, 2H), 3.44–3.51 (m, 1H), 3.62–3.71 (m, 1H), 4.71 (dd, *J* = 5.1, 2.4 Hz, 1H), 9.76 (s, 1H, CHO), $^{13}$C NMR (100 MHz, $CDCl_3$/$CHCl_3$): $\delta$ 13.99, 22.50, 25.53, 28.66, 29.00, 31.61, 33.34, 48.77, 72.93, 80.62, 175.54, 198.02. HRMS (ESI-TOF) (*m*/*z*) [M$^+$+H] calcd for $C_{12}H_{21}O_4$: 229.1440, found 229.1436.
18. Various base-mediated reactions such as $K_2CO_3$/MeOH, KOH/MeOH, DBU/$CH_2Cl_2$, DBU/$CH_3CN$, NaH/THF and NaHMDS/THF were attempted to epimerize the α-carbon centre of aldehyde **27**, but they failed to produce **25**.