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# Synthesis of oxazolidinyl azacycles via ring-closing olefin metathesis: a practical entry to the synthesis of deoxy-azasugars and hydroxypyrrolizidines

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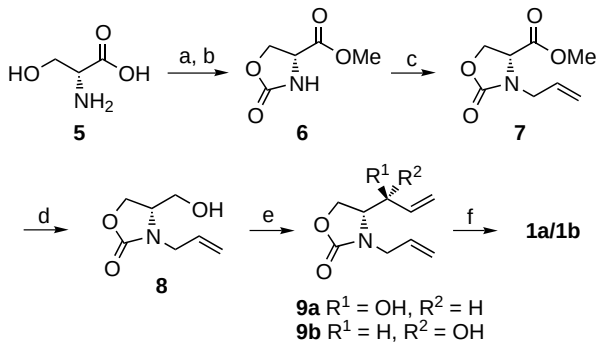
**Abstract**—Starting with D- and L-serines, an expedient method for the preparation of oxazolidinyl piperidines, azepenes and azacyclooctenes was illustrated as a route to various deoxy-azasugars and hydroxypyrrolizidines. The ring-closing olefin metathesis of oxazolidinyl di-olefins was used as a key-step to construct the azacycles. Consecutive epoxidation, hydrolysis and transannulation of oxazolidinyl azacyclooctene led to hydroxypyrrolizidines. © 2001 Elsevier Science Ltd. All rights reserved.

Many (deoxy-)azasugars and hydroxypyrrolizidine alkaloids have been shown to selectively inhibit oligosaccharide processing enzymes.[1] These properties make them potentially chemotherapeutic agents for treating diabetes, cancer, and viral (e.g. HIV and influenza) infections.[1,2] The therapeutic importance of these compounds has stimulated much synthetic effort toward their preparation.[1a,3] Oxazolidinyl piperidine **1a** has recently been reported to serve as an important intermediate for the synthesis of 1-deoxymannojirimycin (**2**) and 1-deoxyaltromycin (**3**) as well as **1b** for 1-deoxygalactostatin (**4**).[4] In addition, compounds **1a**/**1b** can also be used in the synthesis of hydroxylated 2-oxaindolizidines, which are inhibitors of glycosidases[5] (Fig. 1).

However, the literature methods for the synthesis of **1a**/**1b** and their analogs require several steps and resulted in low overall yields.[4,6,7a] As a continuation of our efforts to develop glycosidase inhibitors, we report herein, an efficient and practical synthesis of oxazolidinylpiperidine **1a**/**1b** and their analogs from D- and L-serines. The ring-closing olefin metathesis (RCM) of di-olefin oxazolidinones serves as a key-step in our synthetic schemes. Our method provides diversified stereoisomers that are useful in the SAR study of glycosidase inhibition.




**Scheme 1.** (a) $SOCl_2$, MeOH, reflux, overnight; (b) $K_2CO_3$, triphosgene, $H_2O$/toluene, rt (86% in two steps); (c) NaH, allyl bromide, DMF, 65%; (d) $NaBH_4$, MeOH, 74%; (e) (i) DMSO, $(COCl)_2$, $CH_2Cl_2$, $EtN(i\text{-}Pr)_2$; (ii) vinylmagnesium bromide, $CH_2Cl_2$ (53% in two steps); (f) Grubb's catalyst (10 mol%), $CH_2Cl_2$, rt, 96% (**1a**:**1b** = 1:1.3)

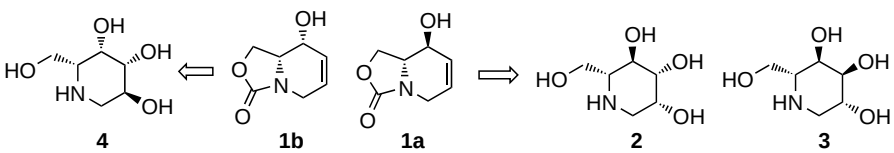


**Figure 1.**

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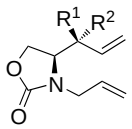
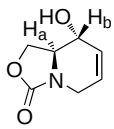
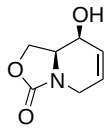
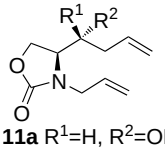
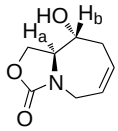
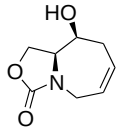
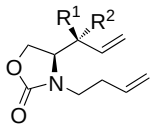
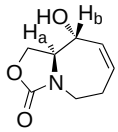
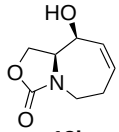
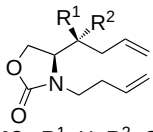
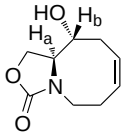
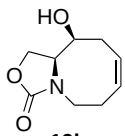
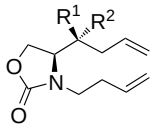
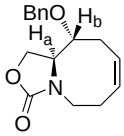
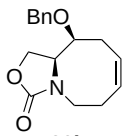
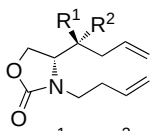
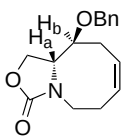
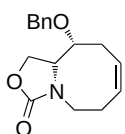
As shown in Scheme 1, D-serine **5** was esterified with thionyl chloride in methanol and then converted into the more stable chiral oxazolidinone **6**[8] by the treatment with triphosgene in the presence of $K_2CO_3$ (86% in two steps). *N*-Allylation of **6** using allylbromide yielded **7** (65%), in which the ester group was subsequently reduced by $NaBH_4$ to give alcohol **8** (84%). Swern oxidation of **8**, followed by addition of vinylmagnesium bromide in a one-pot procedure gave the desired di-olefin compounds **9a**/**9b** as an inseparable mixture (53% in two steps). RCM of **9a**/**9b** using Grubbs' catalyst,[9] $Cl_2(PCy_3)_2Ru{=}CHPh$, (10 mol%) in $CH_2Cl_2$ at room temperature for 2 h afforded quantitative yields of oxazolidinyl piperidines **1a**/**1b** (1:1.3), which were easily separated on a silica gel column. Thus, the important azasugar precursors **1a**/**1b** were prepared in 21% total yield by a six-step sequence.

By a procedure similar to that for **1a**/**1b**, L-serine was converted into di-olefin **10a**/**10b** (Table 1). When allylmagnesium bromide was used instead of vinylmagnesium bromide, di-olefins **11a**/**11b** were obtained. Hydroxyl di-olefins **12a**/**12b** and **13a**/**13b** were prepared by changing the *N*-alkylating agent to 4-bromo-1-

**Table 1.** [a]

| Entry | Reactant | Products *anti* | Products *syn* | Reaction time | *anti*/*syn* (yield) |
|---|---|---|---|---|---|
| 1 |  **10a** $R^1$=H, $R^2$=OH **10b** $R^1$=OH, $R^2$=H |  **16a** $J_{ab}$ = 9.0 Hz |  **16b** | 2 h | 1:1.3 (96) |
| 2 |  **11a** $R^1$=H, $R^2$=OH **11b** $R^1$=OH, $R^2$=H |  **17a** $J_{ab}$ = 7.3 Hz |  **17b** | 5 h | 1:1 (94) |
| 3 |  **12a** $R^1$=H, $R^2$=OH **12b** $R^1$=OH, $R^2$=H |  **18a** $J_{ab}$ = 8.5 Hz |  **18b** | 4 h | 1:1.3 (93) |
| 4 |  **13a** $R^1$=H, $R^2$=OH **13b** $R^1$=OH, $R^2$=H |  **19a** $J_{ab}$ = 8.4 Hz |  **19b** | 24 h[b] | 1:1.2 (21) |
| 5 |  **14a** $R^1$=H, $R^2$=OBn **14b** $R^1$=OBn, $R^2$=H |  **20a** $J_{ab}$ = 9.1 Hz |  **20b** | 4 h | 1:1.2 (64) |
| 6 |  **15a** $R^1$=H, $R^2$=OBn **15b** $R^1$=OBn, $R^2$=H |  **21a** $J_{ab}$ = 9.1 Hz |  **21b** | 4 h | 1:1.2 (64) |

[a]RCM was carried out in 10mol% of catalyst in $CH_2Cl_2$ at rt.
[b]Reaction was slow at rt and heating to reflux resulting in polymerisation of the starting material.

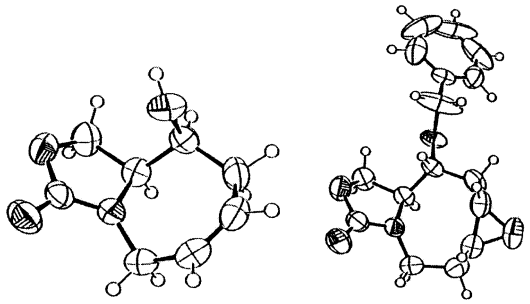
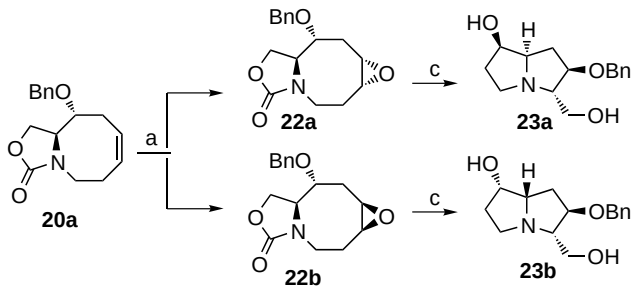



**Figure 2.** ORTEP diagram of compounds **17b** and **22a**.




**Scheme 2.** (a) MCPBA, 81%; (b) LiOH, EtOH/$H_2O$ (1:1), 90°C, 3 h, 73%.

butene and following a similar procedure to that previously described. In addition, the hydroxyl groups of **13a**/**13b** were protected with benzylbromide to give **14a**/**14b**. Similarly, starting from D-serine, compounds **15a**/**15b** were synthesized. As shown in Table 1, the RCM of the di-olefins gave excellent to moderate yields of the corresponding products. However, in the presence of a free hydroxyl group, the formation of the eight-membered ring compounds, **19a**/**19b** from **13a**/**13b**, occurred in low yields (21%, entry 4). The unexpected low reactivity of these compounds may be due to conformational constraint resulting in deactivation of the catalyst by the nearby free hydroxyl group.[10] In order to eliminate the influence of the hydroxyl group, it was protected as the benzyl ether (**14a**/**14b**) with the results showing a significant increase in the yield (64%, entry 5) of product, thus, demonstrating that the hydroxyl group near the olefin plays a role in RCM. It should be noted that this phenomenon was not observed in the cases of formation of six- and seven-membered rings.

The structures of **16a** (*anti*-isomer) and **16b** (*syn*-isomer) were determined by comparing their $^1$H NMR spectra with those of enantiomeric counterparts **1a**/**1b**. Compound **17b**[11] was crystallized from hexane/EtOAc, and the *syn*-configuration was unambiguously determined by X-ray diffraction (Fig. 2). The stereochemistry of the other isomers were established by the $^1$H NMR analysis. For the *syn*-isomers (**18b**, **19b**, **20b** and **21b**), the two protons on the stereogenic carbons did not couple with each other due to their orthogonal disposition.

We also had access to hydroxypyrrolizidine alkaloids by using the eight-membered ring compounds as illustrated in Scheme 2. The compound **20a** was treated with *m*-chloroperoxybenzoic acid to give epoxides **22a** and **22b** (1:1). Compound **22a** was shown by single crystal diffraction to contain the epoxy group on the *exo* face. Treatment of **22a** with LiOH thus provided the desired hydroxypyrrolizidine **23a**[11] in 73% yield as a consequence of oxazolidinone hydrolysis and transannular cyclization.[12] Similarly compound **22b** was converted into hydroxypyrrolizidine **23b**.

In summary, we have successfully converted D- and L-serines to a variety of azacyclic compounds by using ring-closing olefin metathesis as a key-step. This method provides a structural diversity for the synthesis of many stereoisomers of deoxy-azasugars and hydroxypyrrolizidines, suitable for further studies of their glycosidase inhibition.

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## References

1. (a) Stűtz, A. E. *Iminosugars as Glycosidase Inhibitors*: *Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999; (b) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605; (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199; (d) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171.
2. (a) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (b) Davies, G.; Sinnott, M. L.; Wither, S. G. In *Comprehensive Biological Catalysis*; Sinnott, M. L., Ed.; Academic Press: London, 1998; p. 119; (c) van der Broek, L. A. G. M. In *Carbohydrates in Drug Design*; Witczak, Z. J.; Nieforth, K. A., Eds.; Marcel Dekker: New York, 1997; p. 471.
3. *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998.
4. Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, 41.
5. Díaz Pérez, V. M.; García Moreno, M. I.; Ortiz Mellet, C.; Fuentes, J.; Díaz Arribas, J. C.; Cañada, F. J.; García Fernández, J. M. *J. Org. Chem.* **2000**, *65*, 136.
6. (a) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113; (b) Shirai, M.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 5331; (c) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.
7. (a) Martin, R.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 93; (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359.
8. Falb, E.; Bechor, Y.; Hassner, A.; Albeck, A.; Gottlib, H. E. *J. Org. Chem.* **1999**, *64*, 498.
9. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

10. (a) Lin, C.-C.; Subramanian, T.; Hus, T.-S.; Fan, G.-T.; Lin, C.-C. *J. Chin. Chem. Soc.* **2001**, *48*, 55; (b) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444; (c) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.
11. Selected data for **17a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.45–2.60 (m, 2H), 2.86 (br, 1H), 3.53–3.62 (m, 2H), 3.78 (ddd, $J=5.6$, 7.3, 8.6 Hz, 1H), 4.20 (dd, $J=5.6$, 8.9 Hz, 1H), 4.28 (dd, $J=6.8$, 16.7 Hz, 1H), 4.44 (dd, $J=8.6$, 8.9 Hz, 1H), 5.75 (m, 1H), 5.94 (m, 1H). Compound **17b**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.88 (d, $J=10.6$ Hz, 1H), 2.41 (dddd, $J=2.1$, 2.4, 6.5, 15.9 Hz, 1H), 2.76 (dddd, $J=1.0$, 7.0, 7.0, 15.9, 1H), 3.51–3.58 (m, 1H), 3.90 (dddd, $J=2.0$, 2.0, 7.0, 10.6 Hz, 1H), 3.97 (dt, $J=2.3$, 8.2 Hz, 1H), 4.35 (d, $J=8.5$ Hz, 2H), 4.41 (dd, $J=7.2$, 16.8 Hz, 1H), 5.68–5.74 (m, 1H), 5.94–6.00 (m, 1H). Compound **18a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.25–2.35 (m, 2H), 2.48 (br, 1H), 2.92 (ddd, $J=3.4$, 9.6, 16.8 Hz, 1H), 3.63 (ddd, $J=5.6$, 8.5, 14.2, 1H), 3.86 (ddd, $J=3.9$, 8.5, 16.8 Hz, 1H), 4.31–4.37 (m, 1H), 4.34 (dd, $J=5.6$, 9.1 Hz, 1H), 4.41 (dd, $J=9.1$, 8.5 Hz, 1H), 5.77 (ddd, $J=2.04$, 4.2, 13.8 Hz, 1H), 5.91–5.96 (m, 1H). Compound **18b**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.24 (br, 1H), 2.38 (m, 1H), 2.46–2.55 (m, 1H), 3.30 (ddd, $J=2.9$, 8.1, 13.1 Hz, 1H), 3.74 (ddd, $J=3.1$, 8.5, 13.1 Hz, 1H), 4.06 (m, 2H), 4.32–4.40 (m, 2H), 5.94 (m, 1H), 6.03 (m, 1H). Compound **19a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.11 (br, 1H), 2.29–2.40 (m, 2H), 2.42–2.50 (m, 1H), 2.55–2.65 (m, 1H), 3.11 (ddd, $J=3.5$, 8.2, 13.8Hz, 1H), 3.46 (ddd, $J=2.5$, 8.4, 11.50 Hz, 1H), 3.83 (br, 1H), 3.92 (ddd, $J=3.50$, 8.4, 13.8 Hz, 1H), 4.31–4.39 (2H, m), 5.78–5.87 (m, 2H). Compound **19b**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.15 (br, 1H), 2.29–2.65 (m, 4H), 3.19 (ddd, $J=2.4$, 6.3, 13.6 Hz, 1H), 3.88–3.97 (m, 3H), 4.28–4.38 (m, 1H), 4.47 (dd, $J=3.0$, 8.2 Hz, 1H), 5.66–5.73 (m, 1H), 5.78-5.85 (m, 1H). Compound **20a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.29 (ddd, $J=3.0$, 7.3, 7.3, 14.8 Hz, 1H), 2.48-2.58 (m, 3H), 3.05 (ddd, $J=3.0$, 9.2, 13.8 Hz, 1H), 3.50–3.60 (m, 2H), 3.96 (ddd, $J=3.4$, 7.3, 13.8 Hz, 1H), 4.11 (dd, $J=2.0$, 8.8 Hz, 1H), 4.28 (dd, $J=7.3$, 8.8 Hz, 1H), 4.45 (d, $J=11.5$ Hz, 1H), 4.72 (d, $J=11.5$ Hz, 1H), 5.73–5.88 (m, 2H), 7.30-7.38 (m, 5H). Compound **23a**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.0–2.31 (m, 6H), 3.0 (dd, $J=10.1$, 18.8 Hz, 1H), 3.25 (br, 1H), 3.38 (m, 2H), 3.65 (dd, $J=4.4$, 11.3 Hz, 1H), 3.89 (m, 1H), 4.02 (dd, $J=2.5$, 5.1 Hz, 1H), 4.19 (m, 1H), 4.56 (dd, $J=11.5$, 18.6 Hz, 2H), 7.30–7.37 (m, 5H)
12. Harrowven, D. C.; Pattenden, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 3, p. 379.