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RING EXPANDED RAPAMYCIN DERIVATIVES

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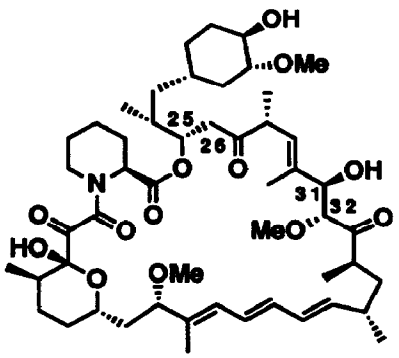
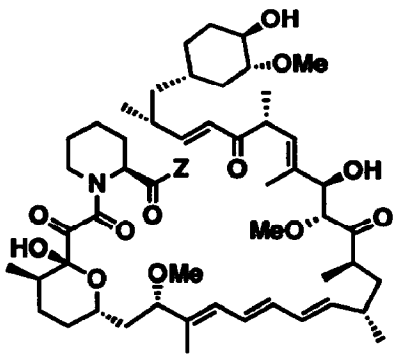
Abstract: Two ring expanded rapamycin derivatives were synthesized from secorapamycin acid via sequential conjugate addition and high dilution macrolactone (lactam) formation.

Rapamycin (1)[1], a complex naturally occuring macrolide antibiotic which possesses a unique immunosuppressive profile, has generated excitement as the result of its potential use in transplantation therapy and the control of autoimmune pathologies. It has numerous sites of chemical reactivity and/or instability and synthetic strategies for the modification of this important molecule must take into account, *inter alia*, an all trans triene, an allylic alcohol, a retroaldol site (C_{31}-C_{32}), a hemiketal masked tricarbonyl unit, and a segment susceptible to β-elimination (C_{25}-C_{26}). This β-elimination pathway to give seco derivative 2 under a variety alkaline conditions has been described in these[2] and other laboratories.[3,4]



1

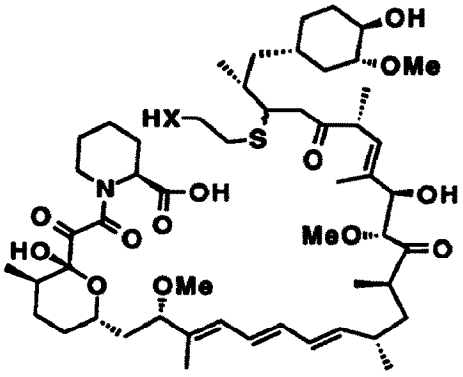


2: Z = OH
3: Z = OR
4: Z = NHR

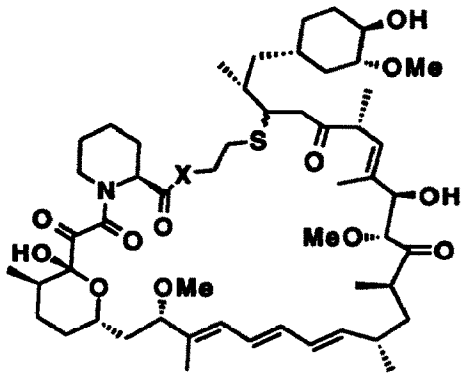
To further investigate the chemistry of seco acid 2 as well as to determine the effect of ring size and shape on immunosuppression, two ring expanded analogs of rapamycin have been designed. Our strategy for the preparation of these compounds involved conjugate addition of an appropriately functionalized thiol to the α,β-unsaturated ketone of 2 followed by macrocyclization. The requisite activation and conversion of the carboxylic acid group of 2 to secorapamycin esters 3 and amides 4 in the presence of the remaining unprotected and highly reactive functional groups has been accomplished.[5]

Reaction of secorapamycin acid 2 with 2-mercaptoethanol in methylene chloride containing 1.1 equivalents of 4-dimethylaminopyridine (DMAP) at room temperature furnished conjugate adduct 5 as a mixture of diastereomers in quantitative yield. Cyclization[6,7] was effected by treatment of 5 with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DAEC), hydroxybenzotriazole (HOBT), and N-methylmorpholine

(NMM) in dimethylformamide (0.02M; 0°C → room temperature) to provide the bishomo thia derivative **6a** (12% yield). Nitrogen isostere **6b** (11% yield) was prepared analogously utilizing 2-mercaptoethylamine.[8]



5a: X = O
5b: X = NH



6a: X = O
6b: X = NH

In summary, we report the first syntheses of ring expanded rapamycin congeners by the interpolation of a three atom segment between lactone oxygen or lactam nitrogen and C_{25}. Secorapamycin acid **2** is a suitable scaffold for this reconstitution affording lactone **6a** and lactam **6b**.

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References and Notes

1. a) Chang, J.Y.; Sehgal, S.N.; Bansbach C.C. *Trends Pharmacol. Sci.* **1991**, *12*, 218-223; b) Kahan, B.D.; Chang, J.Y.; Sehgal, S.N. *Transplantation* **1991**, *52*, 185-191; c) Sigal, H.H.; Dumont, F.J. *Annu. Rev. Immunol.* **1992**, *10*, 519-560; d) Schreiber, S.L. *Science* **1991**, *251*, 283-287.
2. Steffan, R.J.; Kearney, R.M.; Hu, D.C.; Failli, A.A.; Skotnicki, J.S.; Schiksnis, R.A.; Mattes, J.F.; Chan, K.W.; Caufield, C.E. *Tetrahedron Lett.* **1993**, *34*, 3699-3702.
3. Luengo, J.I.; Konialian, A.L.; Holt, D.A. *Tetrahedron Lett.* **1993**, *34*, 991-994.
4. Yohannes, D.; Myers, C.D.; Danishefsky, S.J. *Tetrahedron Lett.* **1993**, *34*, 2075-2079.
5. Skotnicki, J.S.; Kearney, R.M.; Smith, A.L. *Tetrahedron Lett.* accompanying paper in this issue.
6. A macrolactonization under similar conditions to yield a simplified FK-506 analog has been reported: Goulet, M.T.; Hodkey, D.W. *Tetrahedron Lett.* **1991**, *32*, 4627-4630.
7. For examples of macrolactone formation using dicyclohexylcarbodiimide, see: a) Keck, G.E.; Boden, E.P.; Wiley, M.R. *J. Org. Chem.* **1989**, *54*, 896-906; b) Stork, G.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **1987**, *109*, 1565-1567; c) Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P.J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776-2778.
8. Compounds **6a** and **6b** were purified by silica gel flash chromatography and were determined by HPLC analysis to be diastereomeric mixtures containing two major and four major (including amide rotamers) components, respectively; **6a** and **6b** were characterized by CHN, IR, MS, ^{1}H NMR and ^{13}C NMR.

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