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SYNTHESIS OF SECORAPAMYCIN ESTERS AND AMIDES[1]

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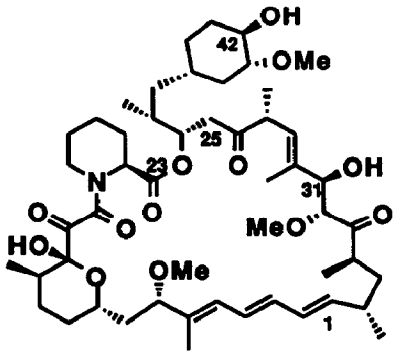
Abstract: Secorapamycin acid has been converted to a variety of functionalized esters and amides. Sequential retroaldol / realdol reaction of a secorapamycin amide provided a truncated analog.

Rapamycin (**1**)[2], a potent macrocyclic immunosuppressive agent currently in Phase I clinical trials for the treatment of transplantation rejection, is a natural product isolated from *Streptomyces hygroscopicus*.[3] The unique and complex molecular landscape of rapamycin consists of a 31-membered ring containing both a lactone and a lactam, a masked tricarbonyl unit, an all trans triene, an allylic alcohol, a β,γ-unsaturated ketone, and 15 chiral centers. We[4] and others[5,6] have shown that under a variety of base catalyzed conditions, rapamycin undergoes facile ring scission via β-elimination to provide secorapamycin acid **2**. To identify potent, efficacious immunomodulators by exploiting this important observation, a series of secorapamycin esters and amides was synthesized.



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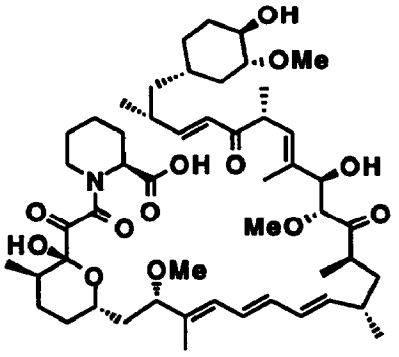
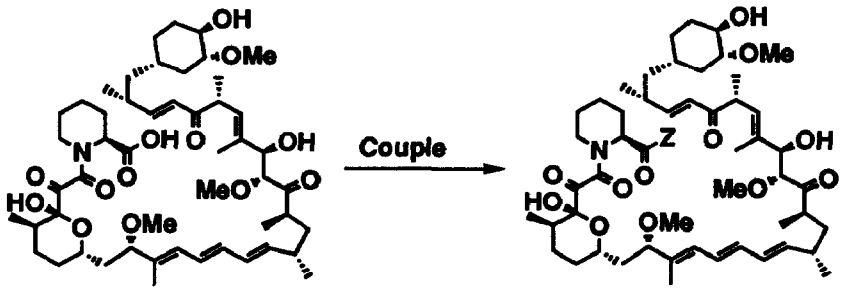


2

The compounds of this study were prepared via modification of the Steglich[7] and Hassner[8] procedures as summarized in Table 1.[9] Treatment of the 4-dimethylaminopyridine (DMAP) salt of secorapamycin acid **2**[4] with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DAEC) and DMAP in methylene chloride containing excess methanol, followed by careful flash chromatography, furnished methyl ester **3a**. Amides **4a-c** were prepared analogously employing the appropriate amine in methylene chloride. An alternate procedure for carboxylic acid functionalization involved the treatment of **2** (free acid) with DAEC, hydroxybenzotriazole (HOBT),[10] N-methylmorpholine (NMM) in dimethylformamide to provide esters **3b-d** and amides **4d-h**. A competing side reaction to produce a spirolactone[11] has been observed during DAEC activation of **2** and may be responsible for the moderate yield of ester and amide products.

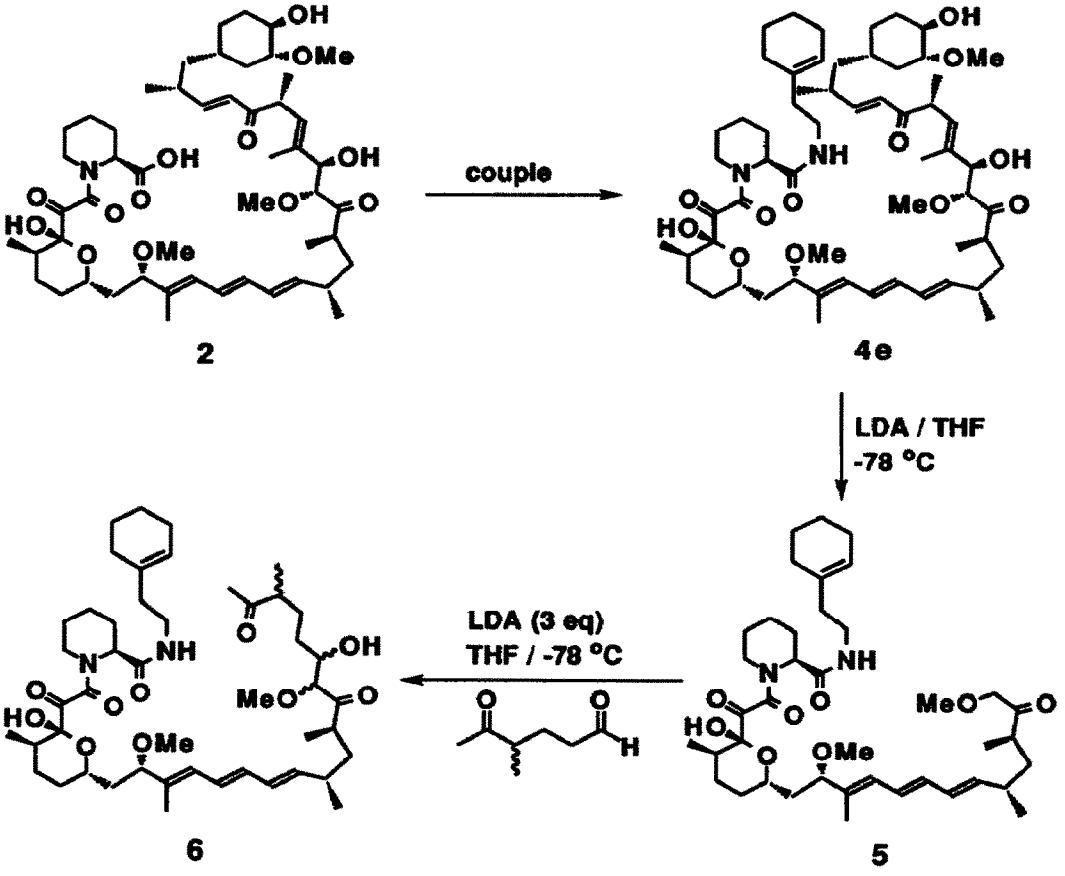
Table 1. Secorapamycin Esters and Amides[9]



Compound	Z	Yield (%)[a]	Method[b]
3a	—OMe	27	A
3b	—OCH_2Ph	41	B
3c	—$O(CH_2)_3$-⬡	29	B
3d	—$O(CH_2)_4$-⬡	21	B
4a	—$NH(CH_2)_3NMe_2$	27	A
4b	—N⬡O	3	A
4c	—$NH(CH_2)_3Me$	46	A
4d	—$NH(CH_2)_3OH$	23	B
4e	—$NH(CH_2)_2$-⬡	30	B
4f	—$NH(CH_2)_3$-⬡	27	B
4g	—$NH(CH_2)_4$-⬡	24	B
4h	—$NH(CH_2)_2$-⬡(OMe, OH)	51	B

[a]Yields reported are for purified (flash chromatography) products and have not been optimized.
[b]Method A: DAEC / CH_2Cl_2 / 40 °C; Method B: DAEC / HOBT / NMM / DMF/ 0 - 25 °C.

Alkyl(cycloalkyl) esters (**3c-d**) and amides (**4e-h**) of varying chain length were designed to mimic the cyclohexyl (C_{23}-C_{42}) region of rapamycin. To eliminate the redundant cyclohexyl region, truncated derivatives **5** and **6** were prepared. Treatment of **4e** with LDA in THF at -78 °C furnished the retroaldol[12] product **5** in 28% yield after flash chromatography. Realdolization was accomplished by condensation of the enolate of **5**, generated with 3 equivalents of LDA in THF at -78 °C, with racemic 3-methyl-5-oxohexanal to afford **6** as a mixture of diastereomers (8% yield after flash chromatography).[13] Thus, compound **6** is a secorapamycin derivative in which the alkyl(cycloalkyl) unit is repositioned on Western half of the molecule and a simplified reconstituted C_{25}-C_{31} segment is introduced on the Eastern half.



2 **4e** **5** **6**

In summary, we have reported the first syntheses of novel esters and amides[14] derived from secorapamycin acid. A truncated secorapamycin amide was designed and synthesized via sequential retroaldol / realdol procedure. The compounds described herein are significantly less potent than rapamycin in the standard in vitro assays.

Acknowledgments: We are grateful to the Analytical Department of Wyeth-Ayerst for spectral, HPLC and microanalytical data. Detailed analyses by Dr. R. Schiksnis and Mr. J. Mattes (NMR), Dr. K. Chan (MS), and Mr. R. Russo (HPLC) are acknowledged. Helpful discussions with Dr. C. Caufield, Dr. A. Failli, Mr. R. Steffan, and Dr. G. Schiehser are appreciated.

References and Notes

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9. The microanalytical, IR, MS, ^{1}H NMR, and ^{13}C NMR data for compounds **3** and **4** are consistent with the assigned structures; compounds **4c**, **5** and **6** were characterized by IR, MS, ^{1}H NMR and ^{13}C NMR. Partial epimerization during the coupling procedure cannot be unequivocally excluded since spectral analysis of these derivatives is complicated by the presence of amide rotamers and an isomer related to the oxepane isomer of Rapamycin (cf. P. Hughes, J. Musser, M. Conklin, and R. Russo, *Tetrahedron Lett.* **1992**, *33*, 4739-4742 and references cited therein).

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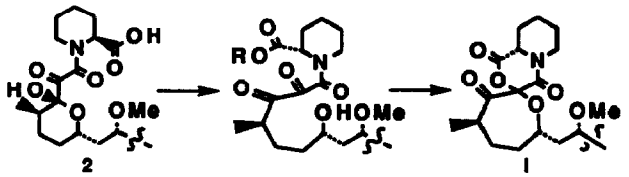
11. Spirolactonization of **2** to furnish **i** under coupling conditions has been reported.[4] A similar spirolactonization of the retroaldol product of **2** was described.[6]



2 i

12. Retroaldol cleavage of secorapamycin acid **2** under analogous conditions has been reported[6] (cf. ref. 4,5).

13. Under these reaction conditions, extensive decomposition was observed; Realdol product **6** consists of two major components as determined by HPLC analysis.

14. In the course of related work Failli and Steffan (unpublished results) also were able to prepare secorapamycin amides with different amino acids using the same DAEC methodology.

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