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DEGRADATION OF RAPAMYCIN: RETRIEVAL OF MAJOR INTACT SUBUNITS.

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Abstract: The degradation of rapamycin has made available key substructures which have defined the structures of advanced synthetic intermediates.

Rapamycin (1) a metabolite of *Streptomyces hygroscopius* was first isolated from Easter Island soil samples.1 It bears a structural similarity to FK-506, which is currently undergoing clinical trials as an immunomodulator.3 While operating at a different cellular signaling level from FK-506, rapamycin is also of interest in immunoregulation.3 Not surprisingly, the research into the biology of rapamycin has brought with it renewed activity at the chemical level.4

Our efforts in probing the chemistry of rapamycin were focused on degradations3 which would retrieve major fragments of the molecule. These products would be examined with respect to their biological activity. They might also serve as subtargets in a total synthesis effort In this regard we were, to some extent, guided by degradative programs which we had developed in the FK-506 series.[6a,b] Our initial successes am recorded herein.

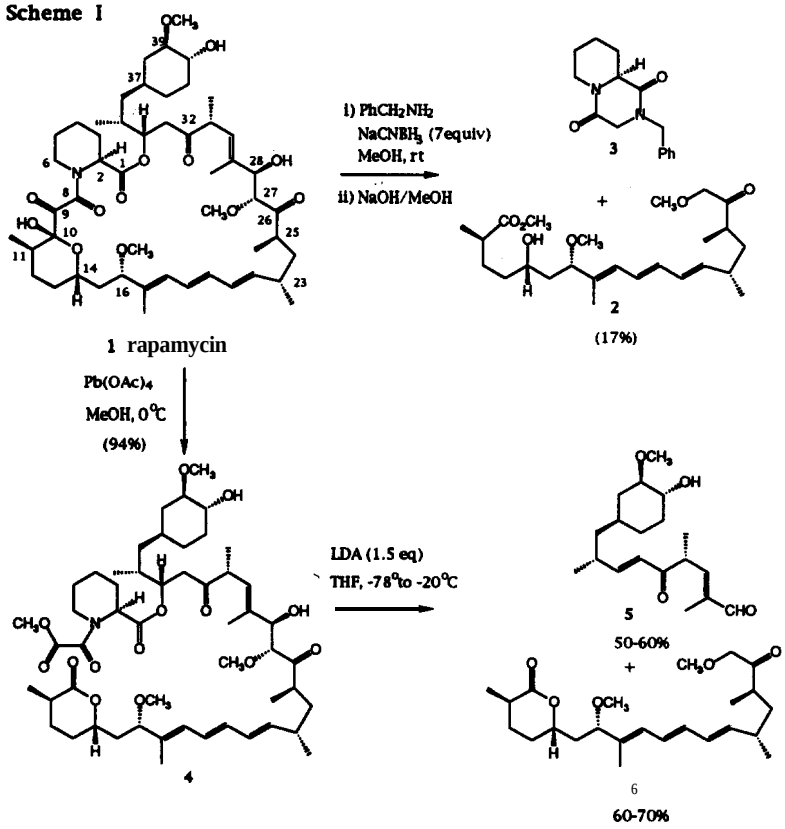
Treatment of 1 with benzylamine and sodium cyanoborohydride (7 equiv.) resulted in reduction of the Cg ketone[6b] and provided a product which, after treatment with methanolic sodium hydroxide, gave rise to a modest yield of keto ester 2. A serious drawback of this protocol was its inability, in our hands, to deliver the C_{28}-C_{42} segment of rapamycin in identifiable form. Another degradation reaction which we had demonstrated in the case of FK-506[6a] was employed to our advantage in the rapamycin series. Treatment of 1 with $Pb(OAc)_4$ in methanol provided seco derivative 4. Exposure of this compound to optimized retroaldol conditions (1.5 equiv. of LDA, THF, -78 °C to -20 °C) effected the cleavage of the C_{27}-C_{28} bond as well as p-elimination of the pipecolinate, thereby affording aldehyde 5 and keto lactone 6 (Scheme I).

Keto aldehyde 9 has been synthesized in our laboratory as a possible intermediate in various projected total syntheses of 1.7 Transformation of degradation fragment 6 into the same (^1H NMR, IR, TLC) compound was accomplished by a four step procedure. Methanolysis of 6 (MnO_2, methanol) followed by silylation of the C_{14} alcohol (TBSCl/imidazole, DMF) afforded keto ester 8. This compound was exhaustively reduced (diisobutylaluminum hydride/CH_2Cl_2) and the resultant product was oxidized to provide 9, thereby confirming our synthetic assignments (Scheme II).

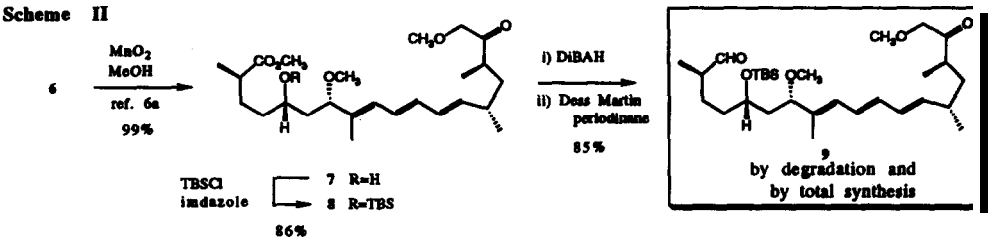
Analysis of the ^{13}C spectrum of 5 obtained by the degradation described above revealed that the stereochemical integrity of C_{31} may have been compromised.3 This problem was attributed to the presence of the vinylogous β-keto aldehyde substructure encompassing carbons 28-32. prior reduction of the C_{32} ketone would alleviate this problem and would also prevent the p-elimination of the C_{34} oxygen under the basic conditions of the retroaldol cleavage. Initial efforts to these ends were directed

to the **reduction** of the C_{32} keto function in the context of cyclic substrate 10 (Scheme III). Sequential (same vessel) silylation of the C_{40} hydroxyl group of rapamycin **(TIPSOTf, 2,6-lutidine, -78°C)** followed by the C_{28} hydroxyl group **(TMSOTf, 2,6-lutidine,** -78 **°C)** afforded 10. Even after extensive variation of experimental conditions for **reduction** of the C_{32} ketone of 10, we obtained at best a 30% yield of 11. Treatment of 11 with $Pb(OAc)_4$ and removal of the TMS ether of 12 **(TBAF/AcOH, THF,** 25 **°C)** provided the retroaldol precursor, 13. A major improvement in reduction efficiency and selectivity was achieved when reaction with lithium **tri-*tert*-butoxy** aluminumhydride was carried out on **seco** derivative 14 ***. Retroaldolization of 13 (1.5 equiv of LDA, THF, -78 °C to -20 °C) afforded*** 15 ***with retention of the C_{34} oxygen function thereby providing access to the intact C_{28}-C_{42} segment of rapamycin (Scheme IV).***

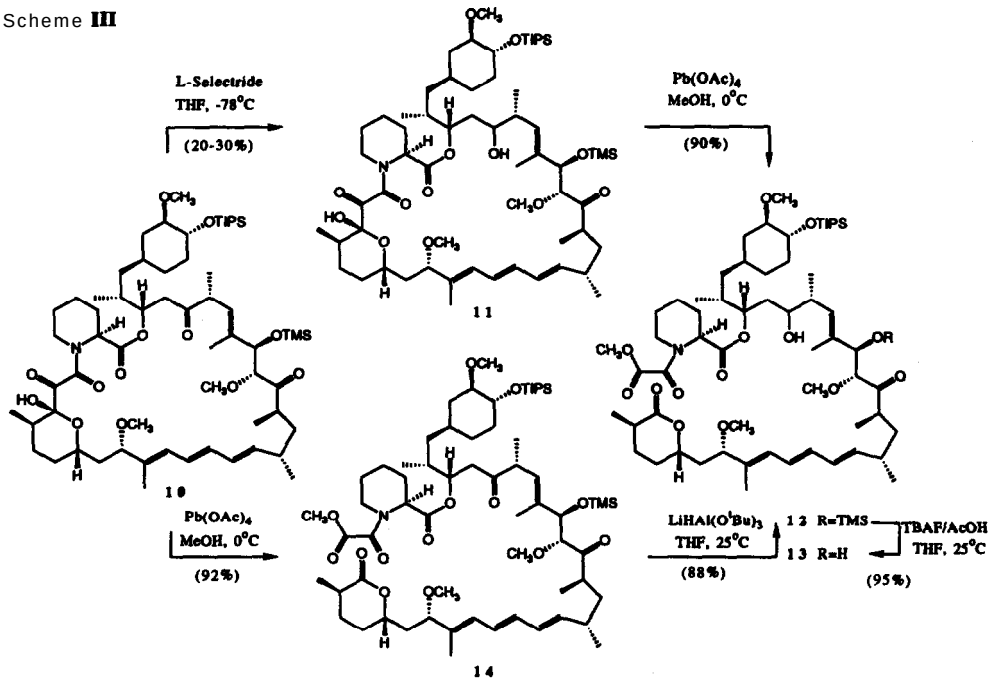
Scheme I



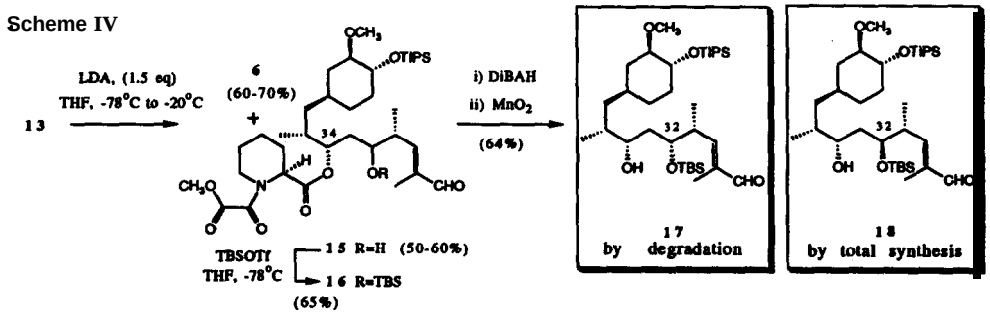
Scheme II



Scheme III



Scheme IV



^{18}A correlation of 15 with fully synthetic material was undertaken. In this way it was hoped to ascertain the configuration of the C_{32} alcohol. The former issue was addressed in a three step sequence which started with silylation of the C_{32} alcohol. Compound 16 was subjected to reductive deacylation of the pipecolinate. Oxidation of the resulting product with MnO_2 afforded compound 17. This substance proved to be similar to, but not identical with the fully synthetic aldehyde 18^{9} possessing, unambiguously, the *S* stereochemistry at C_{32}. Correspondingly, we have assigned the C_{32} stereocenter of 17 to be of the *R* configuration (Scheme IV). Further investigations to explore various strategies for the reconstruction of rapamycin and analogs thereof using these degradation fragments are in progress.

Acknowledgment. This work was supported by NIH Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by NSF Chemistry Division Grant CHE7916210. NIH (CA09059) and Merck Postdoctoral Fellowships to D. Y. are gratefully acknowledged. In addition we would like to thank Dr. Craig Caufield of Wyeth Ayerst Pharmaceutical for providing us with a sample of rapamycin for these studies.

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A General Synthesis of Phosphonic Acid Dichlorides using Oxalyl Chloride and DMF Catalysis

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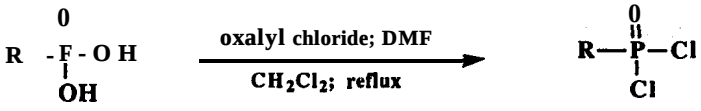
Abstract: A general synthesis of phosphonic diacid dichlorides (1) using oxalyl chloride and catalytic DMF is described.

There are scattered reports in the literature of the synthesis of phosphorous acid chlorides. Those which start from alkylphosphonic diesters use phosphorous pentachloride [1a, 1b] or thionyl chloride2 as the halogenating agent. However, phosphorous oxychloride and ethyl or methylchloride are troublesome side products generated under these conditions, and these reactions suffer from variable yields. Other procedures[3a, 3b] first converted phosphorous alkyl diesters into silyl diesters before reaction with phosphorous pentachloride or oxalyl chloride. In addition to the extra chemical transformation required. one now has a volatile silyl chloride as a side product, which is problematic on large scale. A third approach has been the direct halogenation of phosphonic acids to phosphonic dichlorides. Again, phosphorous pentachloride[4-6] has been widely used, but again, the yields are mixed. Also, in all cases, one must distill the phosphonic dichloride product. Herein is reported an efficient and broadly applicable method for generating phosphonic acid dichlorides (1) on large scale without distillation.

Scheme



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While them are few good methods of monitoring the transformation of carboxylic acids to carboxylic acid chlorides apart from derivitization and analysis. one can accurately follow the conversion of phosphonic acids to phosphonic acid dichlorides by ^{31}P nmr. Typically, the ^{31}P signal is shifted 14 to 20 ppm upfield (see Table), simplifying analysis.

The phosphonic acid starting materials were either obtained from commercial sources or prepared via Arbuzov chemistry6 followed by acid hydrolysis. The DMF-catalyzed reaction of a phosphonic diacid with oxalyl chloride is strongly endothermic and liberates large quantities of gas, as described by the equation:

$$\text{R-P(O)(OH)}_2 + 2\ \text{ClC(O)C(O)Cl} \longrightarrow \text{R-P(O)(Cl)}_2 + 2\text{HCl} + 2\text{C0} + 2\text{CO}_2$$

Distillation of the crude acid chlorides was not required, but is possible via vacuum distillation. Foundistilled acid dichlorides, yields were generally >93%, while distilled yields, when performed for comparison to reported values,[8] were in the range of 85 - 92%. All reagents were obtained from commercial sources and used without

further purification, and all ^{31}P nmrs were recorded at 80.99 MHz on a Varian VXR 200 without internal standard in $CDCl_3$.

Table

$R\text{-}P(O)Cl_2$

R	yield, % crude	yield, % distilled	b.p., °C (mm Hg) found	b.p., °C (mm Hg) lit.[8]	^{31}P nmr peak, ppm $RP(O)Cl_2$	^{31}P nmr peak, ppm $RP(O)(OH)_2$
C_6H_{11}-	94	92	178 (21)	127 (15)	59.6	40.9
C_6H_{11}-CH_2-	95	NA	NA	---	50.8	32.2
C_6H_{11}-$(CH_2)_4$-	94	NA	NA	---	52.6	32.0
CH_2=$CHCH_2$-	92	85	127 (8)	77 (5)	33.1	19.2
C_6H_5-	93	89	107 (4)	105 (4)	37.3	20.9
C_6H_5-CH=$CHCH_2$-	91	NA	NA	---	47.4	23.7

Typical is the synthesis of phenylphosphonic dichloride. A solution of phenylphosphonic acid (2.0 G) and anhydrous DMF (10 µL) was gently refluxed in dichloromethane (30 mL) under dry nitrogen. To this, a solution of oxalyl chloride (2.4 mL) in anhydrous dichloromethane was added, via modified addition funnel.7 During the addition, copious gas was evolved, and heat was applied to keep the reaction temperature at or above 35° C. Upon complete addition of the oxalyl chloride solution, the reaction was held at reflux for approximately one hour, then the reflux condenser was replaced by a still head, and the volatiles (distillation temperature <70° C at 763 mm) were removed. Analysis of the residual brown oil (2.29 G; 93%) by ^{31}P nmr revealed a single peak (see Table), consistent with clean formation of phenylphosphonic dichloride. The product was distilled only for comparison to the literature value.* and could be used without distillation.

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THE CONVERSION OF CARBOXYLIC ACIDS INTO ACID BROMIDES ON BBr_3-MODIFIED ALUMINA

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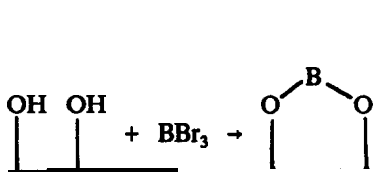
Abstract: Carboxylic acids are converted into acid bromides on alumina which has been modified with boron tribromide. A different reaction occurs in solution.

Acid chlorides are versatile reagents for the synthesis of esters, amides, ketones, and other carbonyl-containing compounds.[1] Acid bromides are less commonly used for these reactions because, unlike acid chlorides, relatively few preparative procedures are available and those that are require brominating agents which are not readily available.[2] We wish to report a new method to prepare acid bromides which is simple to use, versatile, and employs readily available chemicals. The procedure involves treating carboxylic acids with boron tribromide which has been chemisorbed onto alumina (BBr_3/Al_2O_3) (eq.1).

$$RCOOH + BBr_3/Al_2O_3 \rightarrow RCOBr \qquad (1)$$

BBr_3/Al_2O_3 is prepared by treating alumina, which has been activated at 400°C,[3] with a 1.0 M solution of BBr_3 in hexane for 0.5 hours at 0°C.[4] The ratio of the BBr_3 solution to Al_2O_3 is adjusted so that 1 mmol of BBr_3 is chemisorbed per gram of alumina. Copious quantities of gaseous HBr are liberated in the reaction. The reagent, which fumes in air, contains boron (^{11}B SS NMR: broad singlet at 7.1 ppm relative to $NaBPh_4$ at 6 = 0 ppm) and has considerable acidity ($H_o \leq -13.2$).[5] Based on the weight increase of the solid and the (assumed) loss of bromide generated in the chemisorption reaction as HBr, each chemisorbed boron contains one boron-bromine bond (eq. 2)[6] which is the active agent in the formation of acid bromides.



$$+ \quad 2HBr \qquad (2)$$

The reactions, which give moderate to excellent yields of products (Table 1), are run by treating the correspondii carboxylic acids with BBr_3/Al_2O_3 in a 1:1 molar ratio of acid to BBr bonds, ordinarily at room temperature. The reactions can be run in the absence of solvent if the carboxylic acid is a liquid and in solution if the acid is a solid. No starting carboxylic acids were recovered from the reactions.

Table 1. Synthesis of Acid Bromides by the Reaction of Carboxylic Acids with BBr_3/Al_2O_3.[a]

Acid	Solvent[b]	Temperature (°C)	% Yield of Product[c]
Hexanoic	None	RT	67%
Decanoic	Benzene	RT	64%
Benzoic	Benzene	60°	65%
1-Adamantaneacetic	Benzene	RT	70%
p-Nitrophenylacetic	CH_3CN[d]	RT	59%
3-Bromopropionic	CH_2Cl_2	RT	84%
2-Benzoylbenzoic	CH_2Cl_2	RT	86%

a) 40 mmol of RCOOH + 40g of BBr_3/Al_2O_3 (1 mmol BBr_3/g of Al_2O_3) for 20 hours. b) When a solvent was used in the reaction, 100 ml was used. c) Acid bromides, which gave satisfactory spectral data, were converted to methyl esters for yield determinations. d) Acetonitrile reacts with BBr_3/Al_2O_3 in the absence of the carboxylic acid.

Interestingly, reaction of hexanoic acid with neat BBr_3 did not afford the corresponding acid bromide. Instead, the acid was, partially converted to the hexanoic boric anhydride (eq. 3).[7] This result illustrates again that chemistry on a solid may take a markedly different route than the seemingly identical reaction in solution.[8]

$$3CH_3(CH_2)_4COOH + BBr_3 \xrightarrow{\text{solution}} (CH_3(CH_2)_4CO_2)_3B + 3HBr \quad (3)$$

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