Highly Chemoselective Trichloroacetimidate-Mediated Alkylation of Ascomycin: A Convergent, Practical Synthesis of the Immunosuppressant L-733,725

Zhiguo Song,* Anthony DeMarco, Mangzhu Zhao, Edward G. Corley, Andrew S. Thompson, James McNamara, Yulan Li, Dale Rieger, Paul Sohar, David J. Mathre, David M. Tschaen, Robert A. Reamer, Martha F. Huntington, Guo-Jie Ho, Fuh-Rong Tsay, Khateeta Emerson, Richard Shuman, Edward J. J. Grabowski, and Paul J. Reider

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

Received September 4, 1998

L-733,725, a new immunosuppressant drug candidate, was prepared by a highly chemoselective alkylation of the macrolide ascomycin at the C32 hydroxy position with the imidazolyl trichloroacetimidate **16**. The trichloroacetimidate-activated side chain **16** was prepared by an efficient four-step sequence in 42% overall yield. The high chemoselectivity in the alkylation of the C32 hydroxy group of the unprotected ascomycin was the result of the synergetic effects of the electron-donating protecting group on the imidazole **16**, the polar, moderately basic solvent, and the strong acid catalyst. *N*,*N*-Dimethylpivalamide mixed with acetonitrile was found to be the best solvent and trifluromethanesulfonic acid the best catalyst. This synthesis coupled with a resin column purification of L-733,725 followed by crystallization of its tartrate salt has been used to make multi-kilogram quantities of the bulk drug with consistent and high purity.

FK-506 and related compounds are immunosuppressants that have been under development for treatment of rejection of transplanted organs and for psoriasis.[1] Although FK-506 has been approved for clinical use, its toxicity still makes it desirable to find a more potent and less toxic drug. L-733,725 is potentially one such compound under development.[1a,b] The structure of L-733,725, as shown in Scheme 1, consists of two parts, the ascomycin (i.e., L-683,590 or FK-520) macrocycle and an aryl imidazole side chain connected via an ether linkage on C32 of the macrocycle. The synthesis of the macrocycle by chemical or microbial methods is well established, and for the purpose of large-scale production, fermentation is the method of choice.[2] The principal challenge in designing a practical synthesis of L-733,725 is focused upon a suitably activated imidazole side chain and selectively coupling it to the C32 hydroxy group of the macrocycle. A retrosynthetic analysis is shown in Scheme 1. The key steps are the imidazole formation and the ether linkage formation. Two routes to the imidazole portion of the molecule were envisioned. The first one is from the condensation of the aryl glyoxal **1** (hydrate), ammonia, and the aldehyde. The other is via palladium- or nickel-mediated coupling of the aryl halide and the metalated imidazole. Manipulations involving the macrocycle are to be minimized. This convergent route should be more economical than the existing route, where the side chain was built on the macrocycle in a multistep linear fashion.[1a,b]

Results and Discussion

Imidazole Synthesis. One of the classical methods of imidazole synthesis is condensation of glyoxal, ammonia, and an aldehyde unit.[3a] For the preparation of the aryl glyoxal **1** several methods were investigated.[4] Oxidation of the methyl aryl ketone **2** (ArCOMe) by DMSO in the presence of aqueous HBr was chosen and run on a pilot plant scale. The reaction was carried out at 60 °C, and the side product, dimethyl sulfide, was removed with a sweep of nitrogen. The glyoxal monohydrate **1** was crystallized from aqueous DMSO in 77% yield.

Making the imidazole from the aryl glyoxal, ammonia, and an aldyhyde unit proved nontrivial.[3a] As shown in Scheme 2, when glycolaldehyde dimer **4** was used, a 2/1 mixture of the desired imidazole **5** and the imidazole **6** without the hydroxymethyl moiety was produced. Because of the problem in selectively protecting the imid-

(1) (a) Goulet, M.; McAlpine, S. R.; Staruch, M. J.; Koprak, S.; Dumont, F. J.; Cryan, J. G.; Wiederrech, G. J.; Rosa, R.; Wilusz, M. B.; Peterson, L. B.; Wyvratt, M. J.; Parsons, W. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2253. (b) Goulet, M.; Sinclair, P. J.; Wong, F.; Wyvratt, M. J. US Patent 5247076, 1993. (c) Kawai, M.; Gunawardana, I. W. K.; Mollison, K. W.; Hsieh, G. C.; Lane, B. C.; Luly, J. R. *Biiorg. Med. Chem. Lett.* **1998**, *8*, 935. (d) Wagner, R.; Rhodes, T. A.; Ore, Y. S.; Lane, B. C.; Hsieh, G.; Mollison, K. W.; Luly, J. R. *J. Med. Chem.* **1998**, *41*, 1764. (e) Goulet, M. T.; Rupprecht, K. M.; Sinclair, P. J.; Wyvratt, M. J.; Parsons, W. H. *Perspect. Drug Discovery Des.* **1994**, *2*, 145. (f) Van Duyne, G. D.; Standaert, R. F.; Karplus, P. A.; Schreiber, S. L.; Clardy, J. *Science* **1991**, *252*, 839.

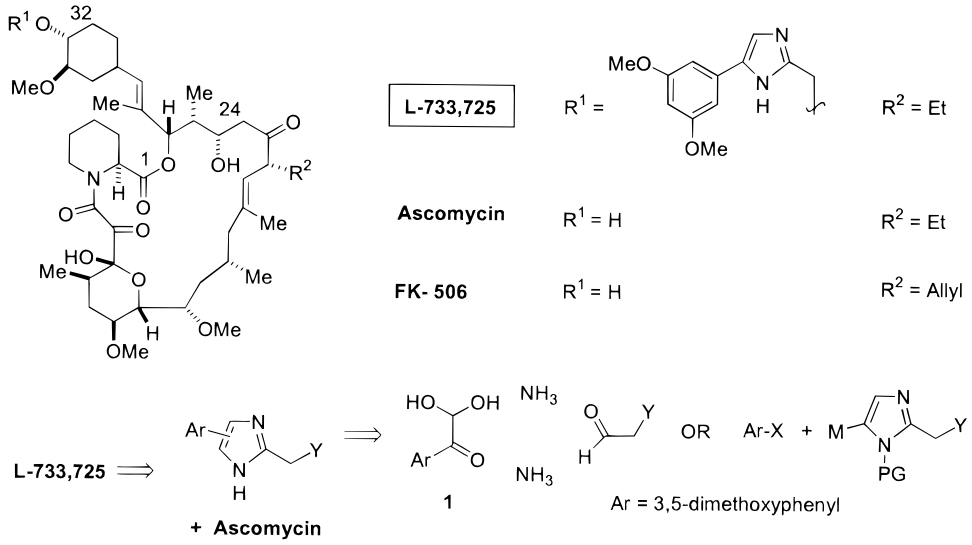
(2) (a) Jones. T.; Reamer, R. A., Desmond, R.; Mills. S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. (b) Byrne, K. M., Shafiee, A.; Nielsen, J. B., Arison, B.; Monaghan, R. L.; Kaplan, L. In *Microbial Metabolites*; Nash, C., Hunter-Cevera, J., Cooper, R., Eveleigh, D. E., Hamill, R., Eds.; Wm. C. Brown Publishers: Dubuque, IA, 1992; Vol. 32, p 29.

(3) (a) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Potte, K. T., Eds.; Pergamon Press: New York, 1984; Vol. 5, pp 457−497. (b) Sigehara, I.; Nakajima, T.; Nishimura, S.; Ohshima, T. EP 365030A1, 1989. (c) Walia, J. S.; Walia, A. S.; Lankin, D. C., Petterson, R. C.; Singh, J. *J. Heterocycl. Chem.* **1985**, *22*, 1117.

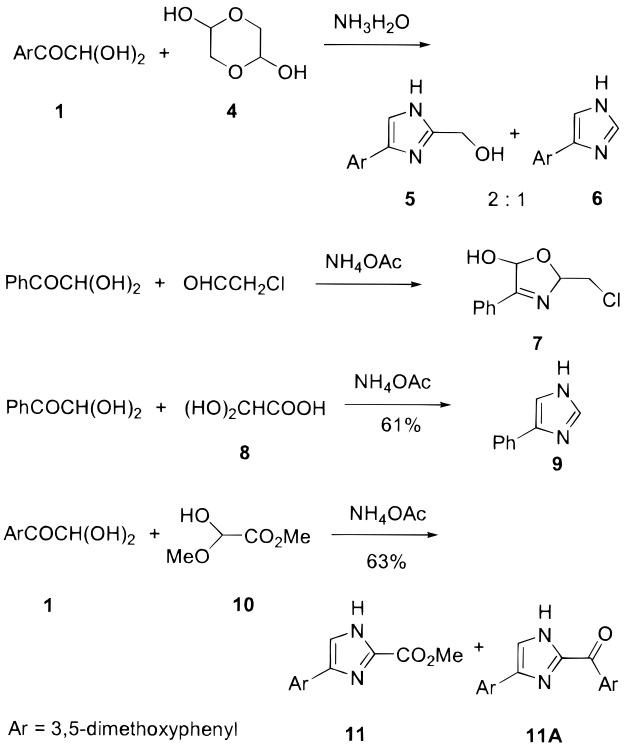
(4) (a) Mikol, G. J.; Russel, G. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 937. (b) Riley, H. A.; Gray, A. R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 509. (c) Desmond, R.; Mills, S.; Volante. R. P., Shinkai, I. *Synth. Commun.* **1989**, *19*, 379. (d) Keifanto, M. M.; Delepine, M. M. *Compt. Rend.* **1962**, *254*, 493. (e) Floyd, M. B.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022.

10.1021/jo981805g CCC: $18.00
Published on Web 02/25/1999

Scheme 1

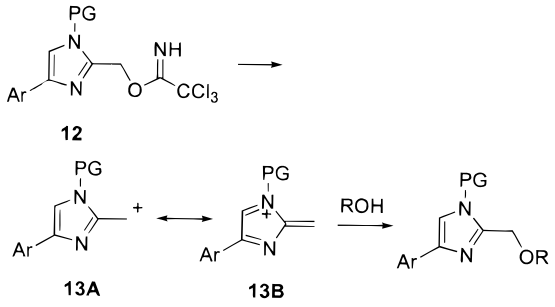


Scheme 2



azole nitrogen of **5** in the presence of the alcohol, this compound is not very useful. When chloroacetaldehyde was used, only the hydrated oxazole **7** was isolated. With glyoxalic acid **8**, only the decarboxylated imidazole **9** was isolated in 61% yield. But when the hemiacetal of methyl glyoxalate **10** was used, the desired aryl imidazole ester **11** was isolated in moderate yield. The major side product was the imidazole **11A** from the condensation of two molecules of the aryl glyoxal with ammonia; thus an excess amount of the methyl glyoxalate **10** had to be used. Fortunately, compound **10** is commercially available at low cost. After considerable optimization, it was found that the best yield for **11** was obtained when the reaction was carried out at neutral pH near 0 °C. As the solvent, the acetonitrile−water mixture was found to give the highest yield and reproducibility. The reaction was carried out by adding a solution of the aryl glyoxal **1** and

Scheme 3

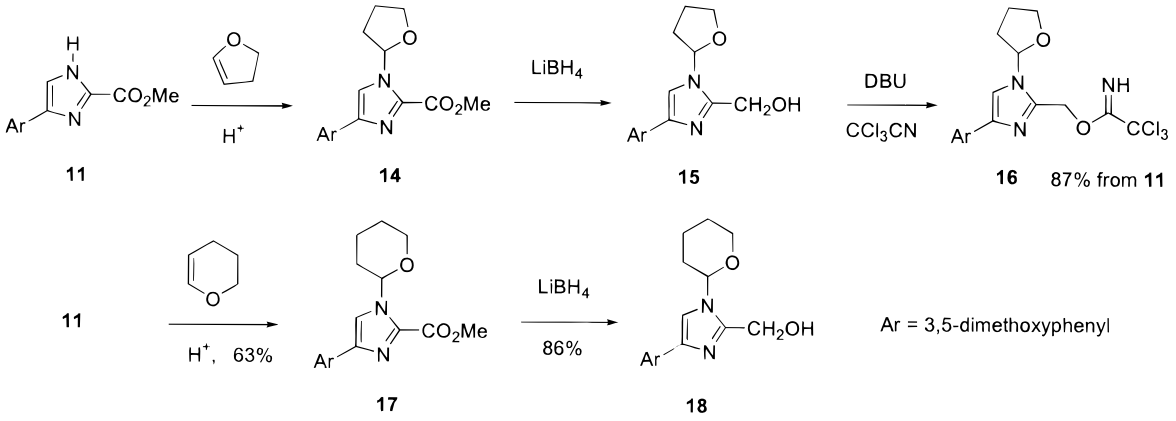


3 equiv of **10** to a solution of 3 equiv of ammonium acetate and 1 equiv of **10** in 1−2 h. The aryl imidazole ester **11** was formed in ~75% assay yield and isolated in 60−65% yield by direct crystallization. The analogous phenyl imidazole ester **11B** (similar to **11** but Ar = Ph) can also be made with the same procedure in 58% yield.

Protecting Group Chemistry. Because of the instability of ascomycin toward strong bases, the ether linkage between the side chain and the macrocycle has to be made under nearly neutral or acidic conditions. Trichloroacetimidate-mediated coupling is the most attractive convergent method for this reason.[5] In addition, a number of trichloroacetimidates have been used successfully to couple alkyl groups with the macrocycle.[1b] In this approach, the active N−H in imidazole **11** is first protected and the ester is reduced to the alcohol. The alcohol is then activated by conversion to the trichloroacetimidate **12** (Scheme 3) to be coupled to the macrocycle. In analysis of the requirements for the imidazole protecting group for the coupling reaction, it was believed that an electron-donating group on the nitrogen might facilitate the trichloroacetimidate cleavage to form the carbonium ion intermediate **13A,B** shown in Scheme 3. Preliminary results in the coupling reaction of cyclohexanol with SEM ($Me_3SiCH_2CH_2OCH_2^-$)[6a] and *p*-toluenesulfonyl-protected imidazole (**12A** where PG = SEM or *p*-toluenesulfonyl) confirmed this hypothesis; that is, the SEM-protected side chain gave a better coupling reaction yield than the tosyl-protected side chain. After some

(5) (a) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *33*, 4139. (b) Schmidt, U.; Respondek, M.; Liebernecht, A.; Werner, J.; Fisher, P. *Synthesis* **1989**, 256.

Scheme 4

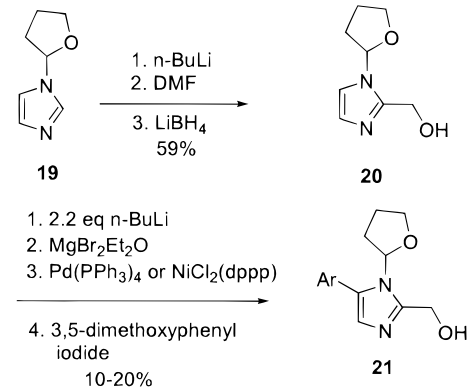


preliminary study and taking into consideration the ease of removal, the 2-tetrahydrofuranyl (THF) and 2-tetrahydropyranyl (THP) groups were the final choices.[6d,e] Thus, as shown in Scheme 4, the THF-protected imidazole **14** was prepared from dihydrofuran and the imidazole **11** with a catalytic amount of acid. Similarly, THP-protected imidazole **17** was prepared from **11** and dihydropyran. The ester groups in both compounds were then reduced to the alcohols **15** and **18** in high yields with $LiBH_4$.

The ease of removal of the THF and THP groups from the imidazole alcohols **15** and **18** was investigated as a model for the similarly protected L-733,725, i.e., the expected coupling product. It is well established that hydrolytic removal of this type of protecting group depends on the electronic effects of the substituents on the imidazole.[6b] The hydroxy groups on **15** and **18** should be good models for the ether group in the expected coupling product (protected L-733,725). At 50 °C with excess tartaric acid in methanol, the half-life for the removal of THF from **15** was 9 h, whereas the half-life for removal of THP from **18** under the same conditions was 54 h. Therefore, THF seemed to be the most suitable protecting group. Thus the alcohol **15** was converted to the trichloroacetimidate ether **16** with a catalytic amount of DBU in 87% overall yield from the ester **11**, as shown in Scheme 4.[5b] Under optimized conditions, imidazole ester **11** was converted to **14** and then reduced to **15** in one pot, and crude **15** was used without purification. The trichloroacetimidate compound **16** was isolated as an easy to handle and stable white crystalline solid.

The alternate, aryl−aryl coupling route to the side chain was also investigated briefly, as shown in Scheme 5. Thus imidazole was protected with the THF group and then lithiated at the 2-position followed by trapping with DMF and reduction, to give the 2-hydroxymethyl imidazole **20**. This compound was then treated with 2 equiv of butyllithium, transmetalated with magnesium bromide, and treated with 3,5-dimethoxyphenyl iodide[8] and a catalytic amount of palladium or nickel complexes.[7] The

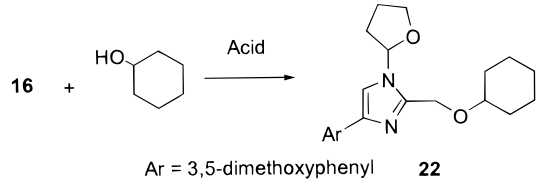
Scheme 5



desired coupling product **21** was isolated in low yields under a variety of conditions with several palladium and nickel complexes. It was later found that the lithiation was sluggish and never went to completion on the basis of deuterium oxide trapping results. Thus when **20** was treated with 2.2 equiv of *n*-butyllithium followed by D_2O, only 56% deuterium incorporation at the 5-position of **20** was observed.

Model Coupling Reaction. With the activated side chain **16** in hand we studied its coupling reaction with cyclohexanol as a model for ascomycin. In the literature, the trichloroacetimidate-mediated coupling has been developed for making benzyl or *p*-methoxybenzyl ethers from alcohols. The most commonly used solvent is methylene chloride/cyclohexane, although diethyl ether has also been used in some cases. Trifluromethanesulfonic acid, boron trifluoride, methanesulfonic acid, and several other acids have all been used as the catalyst.[5]

In our first attempt, we used 10/1 CH_2Cl_2−diethyl ether as the solvent and 1 equiv BF_3−Et_2O as the catalyst. With 2 equiv cyclohexanol, a mixture of products was observed. After column chromatography, only 7% of the desired product **22** was isolated (eq 1). Other fractions



(1)

from the column appeared to be oligomers (by NMR) from the imidazole, presumably by Friedel−Crafts reaction

(6) (a) Brown, R. S.; Manoharan, T. S. *J. Org. Chem.* **1988**, *53*, 1107. (b) Brown, R. S. Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382. (c) Brown, R. S.; Curtis, N. J. *J. Org. Chem.* **1980**, *45*, 4038. (d) Wu, D. C. J.; Cheer, C. J.; Panzica, R. P.; Abushannab, E. *J. Org. Chem.* **1982**, *47*, 2661. (e) Hamamichi, N.; Migasaka, T. *Tetrahedron Lett.* **1985**, *26*, 4743.

(7) (a) Bell, A. S.; Roberts, D. A.; Ruddock, K. S. *Tetrahedron Lett.* **1988**, *29*, 5013. (b) Sekaiya, A.; Ishikawa, N. *Organomet. Chem.* **1977**, *125*, 281. (c) Tamao, K.; Sumitani, K.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. (f) Kalinin, V. N. *Synthesis* **1992**, 413.

(8) Mann, I. S.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 7981.

Table 1. HPLC Assay Yield (%) of 22 from Coupling Reaction between Cyclohexanol and 16 in Different Solvents (Yield Based on 16)

entry	solvents	yield	entry	solvents	yield
1	CH_2Cl_2/ether (10/1)	24	9	MeCN/DMF (10/1)	13
2	CH_2Cl_2/THF (10/1)	32	10	MeCN/*N*-methylpyrrolidone (10/1)	12
3	THF	18	11	MeCN/DMSO (10/1)	28
4	MeCN/THF (10/1)	49	12	MeCN/THF/3-methyl-2-oxazolidinone (10/0.7/1)	48
5	$MeNO_2$/THF (10/1)	51	13	MeCN/Me_2NCONMe2 (10/1)	7
6	MeCN/i-PrCONMe$_2$ (10/1)	58	14	MeCN/DMPU[a] (10/1)	<1
7	MeCN/i-PrCONMe$_2$ (1/1)	65			
8	MeCN/t-ButCONMe$_2$ (1/1)	68			

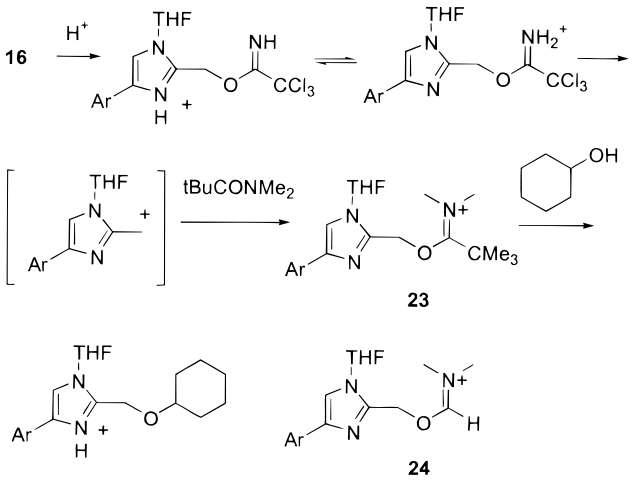
[a] DMPU: 1,3-Dimethyl-3,4,5,6-teatrahydro-2(1*H*)-pyrimidinone.

with the electron-rich dimethoxyphenyl ring. Mechanistically, the reaction presumably goes through a carbonium ion intermediate, which can be trapped either by the alcohol or by the dimethoxyphenyl ring (Scheme 3). Apparently, in this case the selectivity is very low toward ether formation.

Our initial strategy to enhance the selectivity was to stabilize the carbonium ion intermediate by changing to more polar and basic solvents.[9] It is well established that amides are more basic than ethers, which in turn are more basic than nitriles and nitroalkanes.[10] Obviously, it would be necessary to find the solvent that has the most appropriate basicity for this reaction. We started with an extremely strong and nonnucleophilic acid, HBF_4-Et_2O, which we believed would be the best for the reaction, although it had not been used for this kind of transformation before. The coupling reactions were done with 1.4 equiv cyclohexanol and 1.0 equiv HBF_4 at −10 °C in 1 h. The yields of **22** from the coupling reaction in different solvents are summarized in Table 1. Because of the limited solubility of the side chain and ascomycin in some of these solvents, mixed solvents were used in some cases. Methylene chloride, acetonitrile, and nitromethane were tried with ethers, amides, carbamate, ureas, and DMSO as the cosolvents.

As seen from Table 1, great variations (<1% to 68%) were observed with different solvents. Within certain limits, the yield increases with increased basicity and polarity of the solvent. Thus the yield increases according to the order CH_2Cl_2−diethyl ether (entry 1) < CH_2Cl_2−THF (entry 2) < MeCN−THF (entry 4) < MeCN−dimethylpivalamide (*N*,*N*-dimethyl pivalamide) (entry 8). But when the solvent is too basic as with tetramethyl urea or DMPU (entries 14, 15), the reaction did not give any desired product. Apparently, amides have the appropriate basicity for this reaction. Upon screening different amides, it was found that enolizable amides such as *N*-methylpyrrolidinone or the reactive amide DMF also interfere with the reaction. Carbamate (entry 12) was not better than amide. DMSO has a pK_a similar to amides, but the reaction yield in it was low. The best solvent found was *N*,*N*-dimethylpivalamide mixed with acetonitrile, wherein the yield was 68%.

Scheme 6



Different acid catalysts were also compared in the coupling reaction, and it was found that weak acids BF_3 etherate and methanesulfonic acid gave much lower yields than stronger protic acid HBF_4 or trifuromethanesulfonic acid. When the protecting group was SEM instead of THF, the coupling reaction with cyclohexanol in acetonitrile−THF solvent gave similar results. However, when the protecting group was toluenesulfonyl, no desired coupling reaction product with cyclohexanol could be detected. On the basis of NMR evidence, the Friedel−Crafts reaction on the dimethoxyphenyl ring was the dominant reaction. These results confirmed the hypothesis that electron-donating protecting groups can better facilitate the coupling reaction.

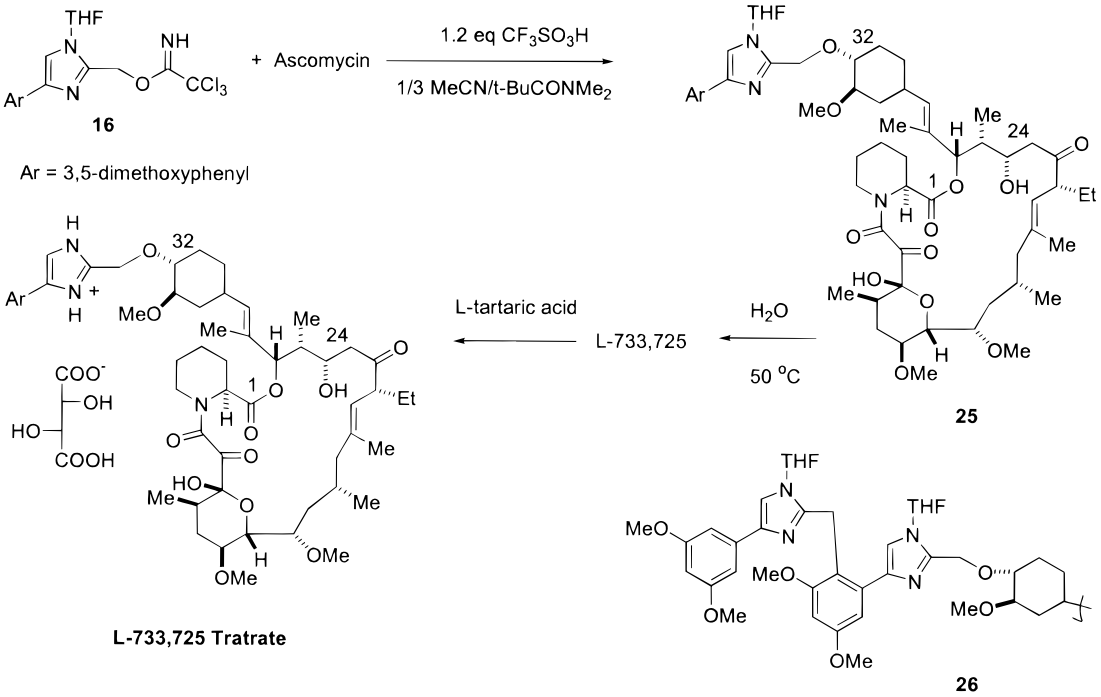
From all the available data, a mechanistic explanation for the dramatic effects of the solvents is proposed as shown in Scheme 6. In the reaction the proton from the acid preferentially protonates the more basic imidazole nitrogen. The proton can equilibrate to the imidate nitrogen to some extent, which leads to the carbon oxygen bond cleavage to generate the carbonium intermediate. When a basic solvent is used as in the case of dimethylpivalamide, the carbonium ion can form a stabilized intermediate like **23**, which will react in a very different manner from a less stabilized carbonium ion.[11] When DMF is the cosolvent, the resulting intermediate **24** could react with alcohol at the less hindered formamide carbon. In the case of *N*-methylpyrrolidone as cosolvent, enolization of the amide in the stabilized carbonium ion intermediate could lead to side products, thus lowering the yield of the desired coupling reaction. When a very strongly basic solvent like tetramethylurea is used, the intermediate may be so stable that it resists any further

(9) (a) Bolton, J. L.; McClelland, R. A. *Can. J. Chem.* **1989**, *67*, 1139. (b) Freedman, H. H. In *Carbonium Ions*; Olah, G. A., Schleyer, P. von R., Eds.; Wiley-Interscience: New York, 1973; Vol. IV, pp 1501−1678.

(10) The known dieclectric constants (*D*) and pK_a values of the conjugate acids for some common solvents are taken from the following references and listed in the format of solvent (*D*, pK_a). H_2O (78, −1.7), CH_2Cl_2 (8.9, −), $MeNO_2$ (35.9, −12), MeCN (37.5, −10), Me_2CO (20.7, −7), EtOAc (6, −6.5), Et_2O (4.3, −3.6), THF (7.6, −2.1), PhCONMe$_2$ (−, −1.6), tButCONMe$_2$ (−, −0.43), MeCONMe$_2$ (38, 0.96), DMF (−, 0), DMSO (−, 0), Me_2NCONMe$_2$ (23, 2.0). (a) Riddick, J. A. *Organic Solvents: Physical Properties and Methods of Purification*; Wiley: New York, 1986; p 536. (b) Arnett, E. M. *Prog. Phys. Org. Chem.*; **1963**, *1*, 324, (pK_a for Me_2NCONMe$_2$ from Merck Index 1989; p 9160).

(11) Julia, M.; Mestdagh, H. *Tetrahedron* **1983**, *39*, 433.

Scheme 7



reaction with alcohol. O-Alkylated amide salts analogous to the proposed intermediate **23** have been isolated and characterized as reported in the literature.[11]

Synthesis of L-733,725. The best conditions for the model coupling reaction were applied to the coupling of the side chain **16** to the unprotected macrocycle ascomycin. These conditions were further optimized relative to stoichiometry, concentration, and reaction temperature. Thus the reaction was carried out by adding 1.2 equiv of trifluoromethanesulfonic acid to a solution of side chain **16** and 1.5 equiv of ascomycin in a 1/3 mixture of acetonitrile−*N*,*N*-dimethyl pivalamide at −30 to 0 °C. Hydrolytic removal of the THF group on the imidazole was realized by addition of water to the reaction and aging at 50 °C overnight. The HPLC assay yield of L-733,725 at this point was 55% based on side chain and 66% based on consumed ascomycin. Most of the unreacted ascomycin can be recovered during the isolation process. The major side product in the coupling reaction was the Friedel−Crafts reaction product **26**, which has been isolated and identified. Ascomycin was moderately overcharged to minimize this side product. Some self-condensation of the side chain by Friedel−Crafts reaction has also been observed. In an attempt to increase the polarity of the reaction media, $LiBF_4$ was added to the reaction mixture (0.2 M $LiBF_4$), but no yield increase was observed. The alkylation reaction is apparently very selective toward the C32 hydroxy group because no alkylation of the less accessible C24 hydroxy and the C10 hydroxy (the lactol) of ascomycin was observed. This unusually high chemoselectivity is the likely result of the synergetic effects of the electron-donating protecting group, the polar and moderately basic solvent, and the strong acid catalyst. Earlier attempts to use the toluenesulfonyl-protected trichloroacetimidate imidazole in the coupling reaction with BF_3-Et_2O as the acid catalyst did not produce any detectable amount of the desired coupling product in methylene chloride.

The crude L-733,725 free amine was isolated as an amorphous solid from the product mixture via an HP-20s resin column in 85% recovery. The purity of L-733,725 at this stage was 95%, which is far below the normal standard for drug manufacturing. Fortunately, the tartrate salt of L-733,725 was found to be stable and crystalline, which is also a pharmocologically acceptable salt. This crystallization by salt formation is a critical step in large-scale manufacturing of the drug because it allows rejection of many low-level impurities which are otherwise impossible to control. Thus, the L-733,725 free amine from the column was converted to the tartrate salt in 94% yield. The purity of the final product was consistently over 98%. The overall yield of L-733,725 tartrate salt is 45% from the side chain and 55% from ascomycin (based on consumed ascomycin). This route is much more scaleable than the existing route because it requires only one resin column purification. The number of reactions involving ascomycin is also minimized to two, coupling and deprotection, thus reducing the chance of producing similar, difficult to separate side products.

In conclusion, a practical, scaleable, convergent route was developed for the synthesis of L-733,725. The properly activated and suitably protected side chain was made in an efficient four-step process in 42% overall yield. The unprotected macrocycle ascomycin was converted to L-733,725 in a highly chemoselective alkylation reaction, which is the result of the synergistic effects of the suitable protecting group, the right solvent, and the proper acid catalyst. Purification via resin column chromatography followed by crystallization as the tartrate salt gave pure L-733,725 suitable for clinical trials. This process has been scaled up to make multi-kilogram quantities of the final drug.

Experimental Section

Reagents and solvents were used as received. All anhydrous solvents were dried over molecular sieves as needed. Karl Fisher (KF) titrations for water contents were carried out on an Aquatest IV moisture analyzer. Melting points were

obtained on a Thomas-Hoover melting point apparatus and uncorrected. Thin-layer chromatography was carried on silica gel 60 plates. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker 250 MHz spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane. Chemical ionization mass spectra (CIMS) were observed with methane as the carrier gas. HPLC columns are 4.6 × 250 mm size, and the packing particle size was 5 μm except as otherwise stated.

3′,5′-Dimethoxyacetophenone was custom-made by Riverside Organic Inc. *N*,*N*-Dimethylpivalamide was custom-made by Chemo Dynamics Inc., or it can be made from 40% dimethylamine in water and trimethyl acetyl chloride and distilled under reduced pressure.

3′,5′-Dimethoxyphenylglyoxal Monohydrate (1). To a round-bottom flask equipped with a nitrogen inlet, a gas outlet to a bleach scrubber, an overhead stirrer, and a temperature probe was charged DMSO (11.3L) and 3′,5′-dimethoxyacetophenone (1.50 kg, 8.32 mol). The solution was heated to 60 °C, and aqueous HBr (48%, 0.873 L, 7.72 mol) was added slowly over 1.0 h via an addition funnel while maintaining the reaction temperature between 60 and 68 °C. A nitrogen sweep was employed to remove the dimethyl sulfide as it was formed. Once the HBr addition was complete, the batch temperature was maintained at 65 °C with external heating until the reaction was complete (typically 6−8 h). The reaction was quenched by adding the reaction mixture into water (20.9 L). The batch temperature was adjusted to 50 °C and extracted with a mixture of toluene (1.67 L) and heptane (1.67 L). More water (20.9 L) was added at 50 °C to the above aqueous layer, and then the batch was cooled to 35 °C. It was seeded and further cooled to 23 °C over 2 h and to 0 °C over another 2 h and aged for 1 h to complete the crystallization. Filtration and washing the wet cake with cold water (21.5 L) followed by air-drying with suction for 24 h afforded 3.29 kg of the title compound as an off-white wet solid, which was 41.7% pure by weight (the rest is water, 77% yield). This wet cake can be used directly in the next reaction. It can also be dried further to constant weight as the monohydrate. Mp > 95 °C (dec). HPLC: Zorbax SB-C18 (3 μm) 3.0 × 150 mm, at 30 °C, 30/70 to 80/20 acetonitrile−0.1% aqueous H_3PO_4 in 10 min, flow = 0.75 mL/min, UV detection at 220 nm, starting material t_R = 5.4 min, product **1** t_R = 2.1 min. ^{1}H NMR (CD_3CN): δ 7.19 (d, J = 2.3 Hz, 2H), 6.76 (t, J = 2.3 Hz, 1H), 5.83 (t, J = 8.4 Hz, 1H), 4.80 (d, J = 8.4 Hz, 2H), 3.82 (s, 6H). ^{13}C NMR (CD_3CN): 196.4, 162.0, 136.2, 108.0, 106.8, 88.1, 56.3. CIMS $MH^+ - H_2O$ = 195.

Anal. Calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70. Found: C 56.61, H 5.83.

2-Chloromethyl-4-phenyl-5-hydroxy-2,5-dihydrooxazole (7). To a round-bottom flask charged with ammonium acetate (0.77 g, 10 mmol), a 50% aqueous solution of 2-chloroacetaldehyde (0.78 g, 5 mmol), and acetic acid (10 mL) was added dropwise a solution of phenylglyoxal monohydrate (0.76 g, 5.0 mmol) while the reaction mixture was stirred. The reaction was stirred overnight, and half of the reaction mixture was concentrated in a vacuum to ca. 5 mL. Solid precipitated out, and it was collected by filtration. The solid was washed with acetic acid (2 × 0.5 mL) and sucked dry, wt 0.21 g (40% yield). Pure sample was obtained by recrystallization from THF−hexane as an amber-colored solid, mp 148−149 °C. ^{1}H NMR (DMSO-d_6): δ 7.90 (d, J = 6.7 Hz, 2H), 7.4−7.6 (m, 3H), 7.30 (d, J = 8.1 Hz, 1H), 6.36 (dd, J = 3.7, 8.0 Hz, 1H), 6.1 (m, 1H), 3.91 (d, J = 3.2 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 168.4, 131.5, 129.7, 128.6, 128.4, 100.6, 99.8, 46.6. CIMS MH^+ = 212.

Anal. Calcd for $C_{10}H_{10}ClNO_2$: C 56.75, H 4.76, N 6.62, Cl 16.75. Found: C 57.00, H 4.76, N 6.64, Cl 16.64.

4 (5)-Phenylimidazole (9). To a round-bottom flask charged with glyoxylic acid monohydrate (0.38 g, 5.0 mmol), ammonium acetate (0.79 g, 10 mmol) in methanol (10 mL), and acetic acid (5 mL) was added dropwise a solution of phenylglyoxal monohydrate (0.38 g, 2.5 mmol) in methanol (12 mL) while the solution in the flask was stirred. After 1.5 h, the reaction mixture was concentrated in a vacuum to a minimum volume of 3−5 mL and was mixed with 0.5 N hydrochloric acid (10 mL). This solution was extracted with 20 mL of ethyl acetate. The aqueous layer was basified with 5 N sodium hydroxide to pH = 9 and extracted with ethyl acetate (20, 10 mL). The combined ethyl acetate layer was dried over $MgSO_4$. The solution was concentrated to dryness to give the title compound as an off-white solid, wt 0.22 g (61%). ^{1}H NMR was identical with 4(5)-phenyl imidazole authentic sample (Aldrich).

2-Carbomethoxy-4(5)-(3′5′-dimethoxyphenyl)imidazole (11). To a reaction vessel equipped with a mechanical stirrer and an internal cooling coil (glycol cooling) were added water (1.0 L), ammonium acetate (1.15 kg, 15 mol), and acetonitrile (10 L). The batch was cooled to 0 °C. In a separate flask fitted with a stirrer was charged acetonitrile (19.5 L), the glyoxal monohydrate **1** (2.56 kg wet cake, assay amount 1.06 kg, 5.0 mol), and methyl 2-hydroxy-2-methoxyacetate (Janssen Chimica, 1.8 kg, 15 mol). All of the solid was dissolved. Then methyl 2-hydroxy-2-methoxyacetate (**10**) (600 g) was added to the first reaction vessel. The glyoxal solution from the flask was added with a continuous flow over 2.0 h, while the reaction mixture was vigorously stirred and kept at 0 °C. Additional acetonitrile (500 mL) was used for rinse. The reaction mixture was stirred for 30 min at 0−5 °C and 22 °C for 1 h. It was mixed with isopropyl acetate (15 L) and washed with 5% sodium bicarbonate (3 × 12 L, gas evolution!) and brine (12 L). The top organic layer was concentrated in a vacuum to ∼8.0 L (bath temp 0−45 °C, >25 in. vacuum). Some of the imidazole product crystallized out. Then isopropyl acetate (3 L) was added and the batch concentrated again to 8 L. This flushing was repeated three to five times until GC showed that the solvent ratio was <8/100 (v/v) acetonitrile−isopropyl acetate when the total volume was ∼11 L. The water content of the supernatant should be less than 3800 μg/mL. Then heptane (10 L) was added and the mixture stirred overnight at 22 °C. The solid was collected by filtration and washed with 1/1 heptane−isopropyl acetate (3 × 1 L) and water (5 × 1 L). It was dried in 50 °C vacuum oven with nitrogen sweep over 2 days to KF ≤ 2000 μg/g. The title compound was obtained as a tan solid, wt 850 g (63%). HPLC 98 wt % purity. TLC R_f = 0.54 (ethyl acetate). HPLC: YMC ODS-AM column; eluents A, MeCN; B, 0.1% phosphoric acid in water; flow 1.5 mL/min. Time 0 A/B 30/70, 10 min 35/65, 20 min 80/20, 25 min 80/20, 26 min 30/70. UV detector at 220 nm. t_R: **11** 6.7 min, **11A** 20.5 min, **1** 4.7 min, glyoxal methanol adduct 9.9 min, isopropyl acetate 7.3 min. Mp: 154−155 °C. ^{1}H NMR ($CDCl_3$): δ 7.49 (s, 1H), 6.93 (s, 2H), 6.44 (t, J = 2.2 Hz, 1H), 4.01 (s, 3H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$ + CH_3COOH): 161.1, 159.9, 139.9, 136.9, 132.2, 122.2, 103.4, 100.7, 44.4, 53.0. CIMS MH^+ = 263.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C 59.54, H 5.38, N 10.68. Found: C 59.37, H 5.15, N 10.58.

2-Carbomethoxy-4(5)-phenylimidazole (11B). The procedure used for preparation of this compound was the same as for the last one, yield 58%. The compound was a white crystalline solid, mp 185−188 °C. ^{1}H NMR (CD_3OD): δ 7.76−7.90 (m, 2H), 7.60 (s, 1H), 7.2−7.4 (m, 3H), 3.95 (s, 3H). ^{13}C NMR (CD_3OD): δ 159.9, 139.0, 129.80, 129.78, 126.5, 52.7. ^{13}C NMR (CD_3OD + CH_3COOH): δ 159.9, 142.5, 139.0, 133.1, 129.8, 128.8, 126.5, 120.9, 52.8. CIMS MH^+ = 203.

1-(2′-Tetrahydrofuranyl)-2-carbomethoxy-4-(3″,5″-dimethoxyphenyl)imidazole (14). To a 3 L round-bottom flask charged with anhydrous THF (1 L) and **11** (50 g, 191 mmol) was added 2,3-dihydrofuran (26.6 g, 380 mmol). The solution was heated to 50 °C, and then a solution of *p*-toluenesulfonic acid monohydrate (1.0 g, 5 mmol) in 10 mL of THF was added. The reaction mixture was stirred at 50 °C for 60 min. After 2 h at 50 °C, the solution was cooled to room temperature. This crude product solution was used directly for the next step without purification. Otherwise, it can be isolated after workup with ethyl acetate and sodium carbonate solution and crystallization from a 1/1 ethyl acetate−hexane mixture as a white solid in 82% yield. TLC R_f = 0.58 (ethyl acetate). HPLC: YMC ODS-AM column, eluents A = MeCN, B = (95% 20 mM phosphate buffer pH = 6.0, 5% MeCN), flow 1.0 mL/min, time 0 A/B 30/70, 10 min A/B 70/30, 20 min 70/30, 21 min 30/70, UV detector at 220 nm. t_R: **14** 12.0 min, **11**

8.2 min, 2,3-dihydrofuran 7.6 min. Mp: 194−196 °C. ^{1}H NMR ($CDCl_3$): δ 7.53 (s, 1H), 6.97 (d, J = 2.3 Hz, 2H), 6.69 (dd, J = 2.2 Hz, 6.4 Hz) 6.4 (t, J = 2.3 Hz, 1H), 4.30−4.40 (m, 1H), 4.05−4.10 (m, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 2.50−2.65 (m, 1H), 1.9−2.2 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 161.0, 159.6, 141.8, 135.0, 134.5, 117.6, 103.3, 100.1, 89.0, 70.36, 55.5, 52.5, 35.2, 23.5. CIMS MH^+ = 333.

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C 61.44, H 6.07, N 8.43. Found: C 61.29, H 6.00, N 8.20.

1-(2′-Tetrahydrofuranyl)-2-hydroxymethyl-4-(3″,5″-dimethoxyphenyl)imidazole (15). The product solution of **14** in THF from last reaction was cooled to −5 °C under nitrogen. To this reaction mixture (cloudy) was added lithium borohydride (4.80 g, 220 mmol). Methanol (7.7 mL, 191 mmol) in 10 mL of THF was added slowly over 10 min (caution: hydrogen gas evolution!). This mixture was stirred at 10−15 °C for 2 h. Then an aqueous NH_4Cl solution (200 g/L, 400 mL) was added slowly (hydrogen gas!). The two layers were separated, and the top organic layer was washed with 40 wt % K_2CO_3 (300 L) solution and then brine (300 mL). This crude product was used directly for the next step, or it can be isolated by crystallization from a 1/1 THF−hexanes mixture as a white solid in 68% for the two steps from the unprotected imidazole. TLC R_f = 0.16 (ethyl acetate). HPLC: same conditions as in the last reaction, t_R = 8.0 min, mp 109−111 °C. ^{1}H NMR ($CDCl_3$): δ 7.13 (s, 1H), 6.85 (d, J = 2.3 Hz, 2H), 6.36 (t, J = 2.3 Hz, 1H), 6.08 (dd, J = 2.8, 6.4 Hz, 1H), 5.05 (br.s, 1H), 4.77 (ABq, J = 3.6 Hz, $\Delta\nu$ = 7.9 Hz, 2H), 4.05−4.15 (m, 1H), 3.90−4.00 (m, 1H), 3.83 (s, 6H), 2.2−2.4 (m, 1H), 2.0−2.2 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 161.0, 147.4, 139.8, 135.6, 112.7, 102.82, 99.4, 85.6, 69.0, 56.8, 55.4, 32.6, 24.5. CIMS MH^+ = 305.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C 59.54, H 5.38, N 10.68. Found: C 59.37, H 5.15, N 10.58.

1-(2′-Tetrahydrofuranyl)-2-trichloroacetimidoxymethyl-4-(3″,5″-dimethoxyphenyl)imidazole (16). The solution of **15** from the last step was concentrated to ∼330 mL and flushed with anhydrous ethyl acetate (KF < 200 μg/mL, 3 × 500 mL). At the end, the residue volume was about 330 mL, and some solid precipitated out. The KF of the supernant was 1000 μg/mL. To this residue was charged ethyl acetate (1.4 L) to dissolve most of the solid. To this mixture were added 25 g of K_2CO_3 powder and trichloroacetonitrile (41 g, 287 mmol). The mixture was stirred for 2 h. The solid was then removed by filtration and the filtrate stirred with more K_2CO_3 powder (12 g) for 0.5 h followed by addition of DBU (0.92 g) in 20 mL of ethyl acetate. The reaction mixture was aged at ambient temperature until completion of reaction (2−4 h). Ethyl acetate (1 L) was added to dissolve all of the product that precipitated during the reaction. The mixture was filtered through Celite (prewashed with ethyl acetate). The clear filtrate was concentrated under vacuum to a thick white slurry (530 g, ca. 550 mL). To this slurry was added heptane (750 mL), and the slurry was stirred for 2 h. The solid was collected by filtration, washed with heptane−ethyl acetate (3 × 50 mL 1.5/1) and heptane (2 × 50 mL), and dried under sweeping nitrogen. The title compound was obtained as a slightly tan, fluffy solid, 75 g (87% yield), mp 148−150 °C. HPLC showed 96.8 wt % pure, >99 area %. TLC R_f = 0.69 (ethyl acetate). HPLC: same conditions as previous reaction t_R = 15.1 min. ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H), 7.32 (s, 1H), 6.94 (d, J = 2.2 Hz, 2H), 6.38 (t, J = 2.0 Hz, 1H), 6.10 (dd, J = 2.6, 6.2 Hz, 1H)5.46 (s, 2H), 4.15−4.25 (m, 1H), 3.95−4.05 (m, 1H), 3.84 (s, 6H), 2.35−2.55 (m, 1H), 2.05−2.30 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 161.9, 161.0, 141.1, 135.8, 113.7, 102.8, 99.7, 90.9, 86.0, 69.2, 63.3, 55.4, 33.5, 24.5. CIMS MH^+ = 448.

Anal. Calcd for $C_{18}H_{20}Cl_3N_3O_4$: C 48.18, H 4.49, N 9.36 Cl 23.70. Found: C 48.09, H 4.37, N 9.43, Cl 24.10.

1-(2′-Tetrahydropyranyl)-2-carbomethoxy-4-(3″,5″-dimethoxyphenyl)imidazole (17). To a round-bottom flask charged with **11** (0.52 g, 2.0 mmol) and 3,4-dihydropyran (1.8 g, 22 mmol) in 10 mL of THF was added *p*-tolunesulfonic acid monohydrate (20 mg). The solution was heated in a 60 °C oil bath for 10 h, and TLC indicated complete reaction. After the reaction mixture was cooled to room temperature, it was transferred to a separation funnel and mixed with ethyl acetate (30 mL) and saturated sodium bicarbonate (20 mL). The two layers were separated, and the organic layer was washed with water (10 mL). The organic layer was concentrated in a vacuum to a solid residue and redissolved in ethyl acetate (20 mL). The solution was filtered through a pad of silica gel. The filtrate was then concentrated in a vacuum to a solid residue, which was triturated with ethyl acetate (4 mL) and hexanes (4 mL). The product was collected by filtration and was dried by sweeping air to a white solid, wt 0.24 g (35%), mp 149−151 °C. A second crop was obtained from the mother liquor by further crystallizing from ethyl acetate (1 mL) and hexanes (3 mL), wt 0.19 g (28%, total 63% yield). TLC R_f = 0.65 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.70 (s, 1H), 6.97 (d, J = 2.3 Hz, 2H), 6.38 (t, J = 2.3 Hz, 1H), 6.2−6.3 (m, 1H), 4.1−4.3 (m, 1H), 3.96 (s, 3H), 3.82 (s, 6H), 3.7−3.8 (m, 1H), 1.95−2.2 (m, 2H), 1.6−1.9 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 170.0, 159.5, 142.3, 134.9, 134.6, 117.6, 103.2, 100.4, 84.8, 68.9, 55.4, 52.5, 33.4, 24.5, 22.8. CIMS MH^+ = 347.

Anal. Calcd for $C_{18}H_{22}N_2O_5$: C 62.42, H 6.40, N 8.09. Found: C 62.45, H 6.41, N 7.80.

1-(2′-Tetrahydropyranyl)-2-hydroxymethyl-4-(3″,5″-dimethoxyphenyl)imidazole (18). It was prepared by reduction with lithium borohydride in the same procedure as for **16** in 86% yield as a hygroscopic white solid, mp > 110 °C. TLC R_f = 0.28 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 6.86 (d, J = 2.3 Hz), 6.35 (t, J = 2.3 Hz, 1H), 5.3−5.4 (m, 1H), 7.77 (ABq, J = 13.6 Hz, $\Delta\nu$ = 16.0 Hz), 4.0−4.15 (m, 1H), 3.82 (s, 6H), 3.65−3.75 (m, 1H), 1.55−2.0 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 169.5, 147.4, 139.4, 135.5, 112.9, 102.7, 99.4, 83.1, 68.4, 56.7, 55.4, 31.4, 24.9, 22.8. CIMS MH^+ = 319.

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C 64.13, H 6.97, N 8.8. Found: C 63.84, H 6.89, N 8.64.

2-Hydroxymethyl-4 (5)-(3″,5″-dimethoxyphenyl)imidazole (5). To a round-bottom flask charged with a solution of **11** (1.0 g, 3.8 mmol) in THF (15 mL) and methanol (0.28 g) was added lithium borohydride solution in THF (2.9 mL 2.0 M). All of this was done under nitrogen. A slight exothermic reaction and gas evolution were observed. More lithium borohydride solution (2.9 mL) and methanol (0.18 g) were added 1.5 h later. After one more hour, water (15 mL) and ethyl acetate (15 mL) were added. The mixture was acidified with 2 N HCl to pH = 1, and the layers were separated. The aqueous layer was basified to pH = 8 with saturated sodium bicarbonate and extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and dried with sodium sulfate. The residue after solvent removal was purified by flash column chromatography (98/2 ethyl acetate−methanol) to gave the title compound as an off-white solid, 0.32 g (36%), mp 193−193 °C. ^{1}H NMR ($CDCl_3$): δ 7.34 (s, 1H), 6.87 (d, J = 2.1 Hz, 2H), 6.35 (t, J = 2.1 Hz, 1H), 4.90 (s, 2H), 3.80 (s, 6H). ^{13}C NMR (CD_3OD+CF_3COOH): δ 163.1, 149.5, 135.0, 129.6, 115.9, 104.5, 102.3, 56.0, 55.8.

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C 61.53, H 6.02, N 11.96. Found: C 61.29, H 6.04, N 11.88.

Kinetics of Solvolytic Removal of THP and THF Groups from Imidazole 15 and 18. In a typical procedure, the THP- or THF-protected imidazole (0.03 mmol) and L-tartaric acid (15 mg, 0.1 mmol) were dissolved in methanol (1.0 mL) and water (0.1 mL). This solution was then stirred at 50 °C, and the reaction was followed by HPLC to at least 50% reaction. The half-life time of the starting material was by direct observation or was calculated by assuming the reaction was first-order to the starting material. HPLC: Zorbax phenyl column, eluents 40% MeCN, 60% (95% 20 mM phosphate buffer pH = 6.0 and 5% MeCN), flow 1.0 mL/min. UV detector at 250 nm. t_R: **5** 4.9−5.2 min, **15** 7.1 min, **18** 9.5 min.

1-(2′-Tetrahydrofuranyl)-2-cyclohexylmethyl-4-(3″,5″-dimethoxyphenyl)imidazole (22). Model Coupling Reaction with Cyclohexanol. Typical procedure: To a dry two neck round-bottom flask equipped with a nitrogen inlet, a temperature probe, and a magnetic stirrer was added **16** (100 mg, 0.22 mmol, KF < 200 μg/g), cyclohexanol (31 mg, 0.31 mmol), anhydrous acetonitrile (3 mL), and *N*,*N*,2-trimethyl

acetamide (0.3 mL, dried over molecular sieves). This solution was then cooled to −25 °C under nitrogen and HBF_4Et_2O (Aldrich 85%, 41 mg, 36 μL, 0.22 mmol) was added via a syringe. The reaction mixture was allowed to cool to −10 to 0 °C and stirred for 1.5 h. The yield of the reaction was determined by taking aliquots and diluted with acetonitrile and injecting into HPLC. The reaction mixture was worked up with ethyl acetate and saturated sodium bicarbonate. Pure coupling product was isolated after purification through silica gel chromatography and eluted with 1/1 ethyl acetate and hexanes. It was further purified by recrystallization from ethyl acetate−hexanes. It is a white solid, mp 100−101 °C. TLC R_f = 0.66 (EtOAc). HPLC: Zorbax phenyl column, eluents 70% MeCN, 30% 0.02 M phosphate buffer pH = 6, flow 1.0 mL/min, UV detector at 250 nm. **22** t_R= 7.2 min. ^{1}H NMR ($CDCl_3$): δ 7.23 (s, 1H), 6.90 (d, J = 2.3 Hz, 2H), 6.35 (t, J = 2.3 Hz, 1H), 6.18 (dd, J = 6.9, 3.2 Hz, 1H), 4.68 (s, 1H), 4.15−4.25 (m, 1H), 3.95−4.05 (m, 1H), 3.82 (s, 6H), 3.3−3.5 (m, 1H), 2.35−2.5 (m, 1H), 1.1−2.3 (m, 13 H).^{13}C NMR ($CDCl_3$): δ 161.0, 144.8, 140.3, 136.3, 113.0, 102.8, 99.4, 85.8, 77.2, 69.1, 62.6, 55.4, 33.4, 32.1, 32.0, 25.7, 24.5, 24.0. CIMS MH^+ = 387.

Anal. Calcd for $C_{22}H_{20}N_2O_4$: C 68.37, H 7.82, N 7.25. Found: C 68.30, H 7.65, N 7.30.

1-(2′-Tetrahydrofuranyl)imidazole (19). To a flask charged with imidazole (15 g, 0.22 mol) and imidazole hydrochloride (7.68 g, 0.074 mol) was added acetonitrile (100 mL) and 2,3-dihydrofuran (42 g, 0.60 mol). This solution was heated to 45 °C for 4 h and then cooled to room temperature. Most of the solvent was then removed under vacuum, the residue was then dissolved in water, and the pH was adjusted to 9 with solid sodium carbonate. This aqueous solution was extracted with methylene chloride (2 × 100 mL). After the methylene chloride layer was dried and the solvent removed under vacuum, a slightly tan oil was obtained, wt 19 g (47% yield). It was used in the next step after drying azeotropically by flushing under vacuum. ^{1}H NMR ($CDCl_3$): δ 7.60 (s, 1H), 7.07 (s, 1H), 7.02 (d, J = 1.0 Hz, 1H), 6.98 (d, J = 1.0 Hz, 1H), 5.89 (dd, 1H, J = 3.0, 6.3 Hz), 3.93−4.14 (m, 2H), 2.0−2.5 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 135.3, 129.9, 116.2, 86.6, 68.9, 33.0, 24.2. CIMS MH^+ = 139.

1-(2′-Tetrahydrofuranyl)-2-hydroxymethylimidazole (20). To a three-neck round-bottom flask charged with **19** (5.0 g, 36 mmol) in anhydrous THF (75 mL), cooled to −20 °C and under nitrogen, was added 1.6 M n-BuLi (25 mL, 40 mmol) solution in hexane. The reaction was aged at −20 °C for 20 min, and anhydrous DMF (2.9 g, 40 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. To this cloudy mixture was added ethanol (75 mL), and the mixture was cooled to −15 °C. Then sodium borohydride (1.37 g, 36 mmol) was added portionwise (exothermic reaction). After the reaction mixture was stirred at room temperature for 1 h, saturated ammonium chloride (50 mL) was added (some forming observed), and the mixture was stirred overnight. Most of the solvents were removed under vacuum to give a slurry residue, which was dissolved in a minimum amount of water. This mixture was worked up with methylene chloride and brine. From the methylene chloride solution, 6.1 g of oil was obtained after solvent removal. Crystallization from 5/1 ethyl acetate−hexane gave the title compound as an off-white solid, 3.6 g (59% yield), mp 89−91 °C. ^{1}H NMR ($CDCl_3$): δ 6.93 (d, J = 1.3 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 6.13 (dd, J = 3.0 Hz, 7.9 Hz, 1H), 5.4 (br, s, 1H), 4.69 (s, 2H), 4.09−4.18 (m, 1H), 3.95−4.05 (m, 1H), 3.36−2.55 (m, 1H), 2.05−2.3 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 147.5, 126.7, 116.4, 85.5, 69.0, 55.9, 33.1, 24.5. CIMS MH^+ = 169.

Anal. Calcd for $C_8H_{12}N_2O_2$: C 57.13, H 7.19, N 16.66. Found: C 56.88, H 7.09, N 16.65.

1-(2′-Tetrahydrofuranyl)-2-hydroxymethyl-5-deuterioimidazole (20-*d*). To a dry three-neck round-bottom flask charged with **20** (168 mg, 1.0 mmol) in anhydrous THF (5 mL) cooled to −65 to 78 °C was added dropwise 1.5 M butyllithium (1.5 mL, 2.25 mmol) in hexanes under nitrogen. A intense brick red color developed after 0.7 mL of butyllithium was added. Some precipitate was also observed. This mixture was stirred at −65 °C for 15 min, and then 60 μL of D_2O was added. The mixture was allowed to warm up to room temperature. The red color faded gradually and a white precipitate was observed as the temperature rose. Then 30 mL of methylene chloride and Mg_2SO_4 was added to the mixture. It was stirred for 2 h and filtered to remove all the solid. The filtrate was concentrated to an oily residue, wt 0.17 g. ^{1}H NMR showed that the peak at 6.93 ppm integrated as 0.44 H, i.e., 56% deuterium incorporation. Some side products were also observed.

3,5-Dimethoxy-1-iodobenzene.[8] It was made from 1-chloro-3,5-dimethoxybenzene by first converting the chloride to the Grignard reagent (in THF), then quenching the Grignard reagent with I_2. It was purified by recrystallization from hexane. ^{1}H NMR ($CDCl_3$): δ 6.85 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H), 3.76 (s, 6H).

1-(2′-Tetrahydrofuranyl)-2-hydroxymethyl-5-(3″,5″-dimethoxyphenyl)imidazole (21). To a 50 mL three-neck round-bottom flask equipped with a temperature probe, a magnetic stirrer, and a nitrogen inlet were added **20** (0.17 g, 1.0 mmol) and anhydrous THF (5 mL). This mixture was cooled to −60 °C and degassed with nitrogen, and 1.5 M *n*-butyllithium (1.46 mL, 2.2 mmol) in hexanes was added dropwise. A brick red suspension developed. After 15 min at −60 °C, magnesium bromide etherate (0.52 g, 2.0 mmol) was added, and the mixture was warmed to room temperature. The mixture became an amber-colored suspension. After it was at room temperature for 15 min, palladium tetrakistriphenylphosphine (30 mg) was added. The mixture was degassed and filled with nitrogen. Then 3,5-dimethoxy-1-iodobenzene (264 mg, 1.0 mmol) was added as a solution in 2 mL of anhydrous and degassed THF. The mixture was stirred at 50 °C for 20 h. After it was cooled to room temperature, the mixture was mixed with ethyl acetate (20 mL), 0.l M EDTA disodium (10 mL), and saturated ammonium chloride (20 mL). After the two layers were separated, the aqueous layer was extracted with ethyl acetate (20 mL) and methylene chloride (20 mL). The combined organic layer was concentrated in a vacuum to remove all solvents. The residue was mixed with methylene chloride (20 mL) and water (10 mL). After the two layers were separated, the organic layer was concentrated to an oily residue, wt 350 mg. ^{1}H NMR ($CDCl_3$) indicated the molar ratio of the desired product to the starting iodide was 1.0/2.4 (30% conversion). A small amount of the title compound was isolated from the crude products through silica gel chromatography (eluted with 2% MeOH−EtOAc) of similar runs as a half solid. ^{1}H NMR ($CDCl_3$): δ 6.84 (s, 1H), 6.49 (d, J = 2.3 Hz, 2H), 6.44 (m, 1H), 6.2 (br. s, 1H), 4.74 (ABq, 2H), 4.05−4.10 (m, 1H), 3.7−1.9 (m, 1H), 3.76 (m 6H), 2.2−2.4 (m, 2H), 1.9−2.1 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 160.6, 148.7, 133.7, 131.9, 126.2, 108.0, 100.3, 86.5, 68.4, 60.4, 56.7, 55.4, 32.2, 25.2. CIMS MH^+ = 275.

L-733,725 Tartrate: Coupling Reaction. To a 72 L round-bottom flask was charged **16** (1.30 kg 2.90 mol), ascomycin (3.448 kg, 4.35 mol, 1.5 equiv, produced in house by Merck, 98%), and *N*,*N*-dimethyl pivalamide (*N*,*N*-dimethyl pivalamide, 19.5 L). The KF was 2400 μg/mL for the solution. It was dried by adding acetonitrile (10 L, KF = 100 μg/mL) and removing it under vacuum at 15−25 °C/29 in. Hg vacuum). The solvent flush with CH_3CN was repeated twice (final KF = 50 μg/mL). The reaction mixture was diluted with CH_3CN (6.5 L) and cooled to −33 °C under N_2. Then trifluoromethanesulfonic acid (i.e., triflic acid, 522 g, 3.42 mol) was charged into the batch. The reaction mixture was warmed to 0 °C over 3 h. Then water (6.5 L) was added, and the pH of the reaction mixture was adjusted to 2−3 with triflic acid if it was higher. The mixture was heated to 50 °C for 24 h. The mixture was cooled to room temperature and mixed with ethyl acetate (13 L) and saturated sodium bicarbonate (6.5 L). The two layers were separated, and the organic layer was washed with brine (6.5 L). The combined aqueous layer was extracted with 6.5 L of ethyl acetate. The combined organic layer was concentrated in vacuo to a minimum volume and flushed with acetonitrile (12 L, the residue had a KF = 7% water). The residue was flushed with 2-propanol (15 L and 5 L) to a KF = 0.37% water. The residue was then flushed with acetonitrile (10 L), diluted with acetonitrile (40 L), and extracted with hexane (4 × 80 L). The desired L-733,725 stayed in the lower acetonitrile

layer, and the dimethyl pivalamide was extracted into the hexane layer. The acetonitrile layer was concentrated in vacuo to a minimum volume as a thick brown oil, wt = 12.8 kg. HPLC analysis showed it contained 12.5% L-733,725 by weight. The yield of L-733,725 was 1.60 kg (55% based on **16**, 66% based on ascomycin consumed). Other compounds in the mixture include ascomycin (1.9 kg, 45% of the charge), the overalkylation product, i.e., **26** without the THF protecting groups (8.3% relative to the L-733,725 peak at 215 nm), plus *N*,*N*-dimethyl pivalamide. HPLC: YMC ODS-AM column at 50 °C, A MeCN, B 0.1% H_3PO_4 in water, flow rate 1.2 mL/min. Time 0 A/B 30/70, 10 min A/B 60/40, 40 min A/B 70/30, 50 min A/B 80/20, 51 min A/B 30/70. t_R: THF-protected L-733,725 **25** 23.7 min, ascomycin 26.4 min, overalkylation product **26** (THF protected) 35.1 min, L-733,725 17 min, deprotected **26** 19.2 min.

Small amounts of the desired coupling reaction product **22** and the bisalkylation side product **23** were isolated by quenching the coupling reaction mixture before water addition with saturated sodium bicarbonate solution and separating the organic products through silica gel column chromatography. They were isolated in ~90% purity and were partially characterized. **25:** ^{1}H NMR ($CDCl_3$): δ (peaks over 5.5 ppm) 7.22 (s, 1H), 6.88 (d, J = 2.1 Hz, 2H), 6.32 (t, J = 2.1 Hz, 1H), 8.26−6.28 (m, 1H). Electron spray ionization MS M^+/e = 1078. **26:** ^{1}H NMR ($CDCl_3$): δ (peaks over 5.5 ppm) 8.22−8.25 (m, 1H), 7.14 (s, 1H), 6.90 (m, 3H), 6.37 (d, J = 2.5, 1H), 6.30 (m, 2H), 6.1−6.2 (m, 2H). Electron spray ionization MS M^+/e = 1364. TLC (EtOAc) **25** R_f = 0.43, **26** R_f = 0.50.

HP-20S Resin Purification. The HP-20S dry resin (32 L) was swelled with acetone (40 L) for 1 h, then loaded onto a chromatography column. The column was eluted with acetone (72 L), acetonitrile (72 L), and 1/1 acetonitrile−water (72 L). The column was allowed to age for 18 h. The final volume of resin was 36 L. The crude batch of L-733,725 free base was divided into two portions of 6.3 kg each. Each portion contained 787 g of L-733,725 by HPLC assay. One portion was dissolved in 50/50 CH_3CN-H_2O (90 L), and this solution was loaded onto the resin column at a rate of 2 bed volumes per hour. The column eluent was collected in 36 L cuts (one bed volume). Once loaded, the column was eluted with 50/50 CH_3CN-H_2O up to fraction 14. The column was then eluted with 60/40 CH_3CN-H_2O from fractions 15−23. Fractions 4−7 contained ascomycin, and fractions 14−23 contained L-733,725. Fractions 15−20 were combined, and solid NaCl (11 kg) was added. After 40 min of stirring, the layers were allowed to separate. The upper organic layer (108 L) showed 756 g of L-733,725 by HPLC assay. The organic layer was concentrated in vacuo to afford an oil suspended in about 10 L of water. The batch was extracted with ethyl acetate (10 L), and the organic was passed through a pad of silica gel (1.5 kg). The aqueous was reextracted with fresh ethyl acetate (2 × 10 L), and each extract was filtered through the pad of silica gel. The filtrate was concentrated in vacuo to afford a foam. The foam was dried under vacuum (29 in. Hg/25 °C) for 18 h. The dry batch weighed 716 g and was 95% pure by weight (86% recovery on column). The column was washed by eluting it with acetone (72 L) and acetonitrile (72 L) at a rate of 2−3 bed volumes per hour. The column was reequilibrated with 50/50 acetonitrile−water (72 L), allowed to age for 18 h, and used again.

L-733,725 Tartrate Salt Formation. In a 50 L flask containing L-733,725 free base (1.45 kg at 80% purity, 1.16 kg, 1.15 mol) was added acetonitrile (7 L; KF = 15 μg/mL), ethyl acetate (6.5 L; KF = 50 μg/mL), and water (140 mL) to form a 1% aqueous solution. To the batch was added l-tartaric ((2*R*,3*R*)-(+)-tartaric acid, 215 g, 1.43 mol). The mixture in the flask became cloudy within 10 min, and the tartaric acid dissolved within 1 h. The batch was seeded with 4 g of L-733,725 tartrate salt. The mixture was stirred at room temperature, under N_2 for 18 h. A sample of the mother liquors showed 12.3 mg/mL of product. The thick white slurry was collected by filtration and washed with pure ethyl acetate (2 × 1 L). It was dried first with sweeping air and then in a vacuum oven on glass trays at 50 °C with a nitrogen sweep for 8 h. This afforded 1.26 kg (94% recovery) of a white solid which was 98.5 area % on HPLC. HPLC: YMC ODS-AM column at 50 °C, eluent A MeCN, B 0.1% H_3PO_4 in water, time 0 A/B 50/50, 30 min A/B 80/20, flow = 1.0 mL/min, UV detection at 215 nm. L-733,725 exhibits three peaks on reverse phase HPLC, a major peak of ~95% and two minor equilibrium peaks; major peak t_R = 17 min, minor peaks t_R = 16.2 min, 12.4 min, over alkylation product (deprotected **26)** t_R = 19.4 min. The product area % includes the main peak and the equilibrium species peaks. Mp = 165.5 °C. $[\alpha]_{365}$ = 607° (25 °C, 1.0% in MeOH). Two sets of peaks were observed on the ^{13}C NMR of ascomycin and L-733,725. They are believed to arise from two rotational isomers. ^{13}C NMR (100.61 MHz, acetone-d_6, major rotational isomers): δ 211.9, 198.0, 173.3, 169.9, 166.2, 162.1, 147.7, 139.4, 138.9, 136.6, 133.1, 132.2, 124.7, 115.9, 103.4, 99.5, 98.1, 84.0, 82.5, 79.7, 76.2, 74.4, 73.6, 72.9, 70.3, 65.6, 57.4, 57.3, 57.2, 56.4, 55.5_9, 55.5_8, 49.8, 46.6, 41.1, 39.6, 36.9, 35.5, 35.4, 34.2, 33.4, 31.3, 30.7, 28.5, 26.9, 25.3, 25.2, 21.9, 20.2, 16.6, 16.0, 13.6, 11.9, 10.3. ^{1}H NMR (400.13 MHz, acetone-d_6, selected data, major rotamer): δ 7.50 (s, 1H), 6.97 (d, J = 2.3, 2H), 6.35 (t, J = 2.3, 1H), 5.25 (d, J = 4.8, 1H), 5.21 (br d, J = 9.1, 1H), 4.95 (br d, J = 10.3, 1H), 4.77 (s, 2H), 4.63 (br t, J = 3.6, 1H), 4.54 (s, 2H), 4.34 (br d, J = 13.1, 1H), 3,97 (m, 1H), 3.80 (s, 6H), 3.71 (dd, J = 9.5, 1.2, 1H), 3.63 (m, 1H), 3.45 (s, 3H), 3.37 (s, 3H), 3.32 (s, 3H), 2.95 (td, J = 13.1 3.2, 1H), 2.79 (dd, J = 14.3, 5.6, 1H), 1.68 (d, J = 1.2, 3H), 1.62 (d, J = 1.2, 3H), 0.94 (d, J = 6.3, 3H), 0.92 (d, J = 7.1, 3H), 0.90 (d, J = 6.7, 3H), 0.82 (t, J = 7.5, 3H).

Anal. Calcd for $C_{59}H_{87}N_3O_{20}$: C 61.10, H 7.50, N 3.60. Found: C 60.85, H 7.66, N 3.63. Electron spray ionization MS M^+/e = 1008.

JO981805G