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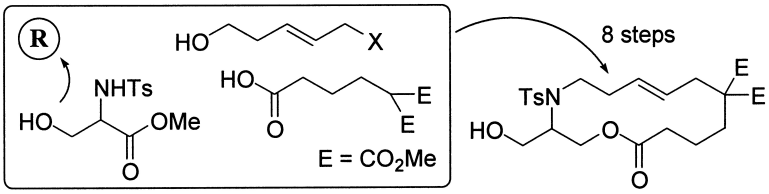

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Solid Phase Combinatorial Synthesis of a Library of Macro-Heterocycles and Related Acyclic Compounds

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A solid phase synthesis of macrolactones from three building blocks and in eight steps is described. The synthesis which is carried out on the DHP resin includes Mitsunobu and DIC couplings. The macrocyclization occurs by SN2 displacement of an allylic chloride by a malonate anion. The synthetic methodology is suitable for the synthesis of arrays of macrocycles as well as linear compounds.

Introduction

The solid phase synthesis of macro-heterocycles[1] is of significance to drug discovery and is an active area of research. Macrolides[2] have been used as pharmaceuticals and are therefore attractive targets for the solid phase synthesis of combinatorial libraries. The solid phase syntheses of taxol[3] and epothilone[4] analogues have been described.

To produce a potentially diverse combinatorial library of macro-heterocycles using solid phase techniques, it is important to design a synthesis in which at least three components can be independently and readily varied. Our research group has already described a powerful and versatile approach,[5] and the purpose of this work is to apply this technology to prepare a library of 96 macrocycles and linear equivalents.

Design of the Library

The original route (Scheme 1) previously described by us[5] would allow the synthesis of the macrocycles such as **1** in only six steps. However, we reasoned that the allylic chloride key building block **2** or other related allylic, propargylic, or benzylic chlorides could be rather unstable in some cases, and this might be detrimental to the synthesis of large diverse libraries in a reliable way. To design a more general route, it was therefore necessary to eliminate the use of such reactive compounds. The new route which was designed is only two steps longer and all building blocks are now sufficiently stable such that they can be prepared on large scale and stored over long periods of time. It is worth noting that the order of introduction of the two last building blocks has been inverted, demonstrating the high flexibility of the chemistry involved.

The goal of the work was to build a library of 96 members, among which 24 are macrocycles and 72 are linear products (Table 1). Both types of compounds are made from three sets of building blocks: (1) six suitably protected α-amino acids (Ts-Ser-OMe, Ts-Thr-OMe, Ts-Tyr-OMe, $PhSO_2$-Ser-OMe, $PhSO_2$-Thr-OMe, and $PhSO_2$-Tyr-OMe) which are subsequently reduced to amino alcohol derivatives and are found at the RAA (reduced amino acid) position in the final products (**A** to **F**), (2) four monoprotected diols (alcohol at the allylic position protected by TBDPS) (HO-**G**-OTBDPS, HO-**H**-OTBDPS, HO-**I**-OTBDPS, and HO-**J**-OTBDPS) that are located at the L1 (linker 1) position in the members of the library (**G** to **J**), and (3) four acids (HO-**K**-H, HO-**L**, HO-**M**, and HO-**N**) which are coupled to the RAA parts by ester bonds and which are found at the L2 (linker 2) position in the end products (**K** to **N**). One of these four acids (HO-**K**-H) bears a malonate moiety and is therefore the only L2 building block which can lead to macrocycles by linking L1 with L2.

Results and Discussion

A new investigation was carried out in solution in order to find an alternative route to the less reliable allylic chloride approach. The macrocycle **AGK** (**1**) was chosen as the target molecule for that investigation. The eight steps necessary to obtain **AGK** were carried out as shown in Scheme 2. This compound was first prepared in solution using a benzyl group to replace the polystyrene polymer. This strategy was used to establish good experimental conditions for each individual step including the macrocyclization.

The protected serine **3**[5] was hooked to DHP resin mimic **4** (Scheme 2) under mild acidic conditions[6] to obtain the corresponding ether **5** (benzyl instead of polystyrene) in 89% yield. Then the alcohol **6**[7] was attached at the tosylamide end of the previous molecule under Mitsunobu[8] conditions in 81% yield to provide **7**. Step 3 consisted in the reduction of the methyl ester group by means of lithium aluminum hydride,[9] and the alcohol **8** was obtained in 79% yield. The last building block **9**[5] was then coupled to the alcohol **8** with DIC[10] (87% yield) to give the triester **10**. The silyl ether was cleaved at step 5 with tetrabutylammonium fluoride (96% yield), and the resulting alcohol **11** was transformed into the corresponding allylic chloride with carbon tetrachloride and tributylphosphine with a yield of 91%. This new method of preparing the allylic chlorides generated higher yields in shorter reaction times and was preferred over

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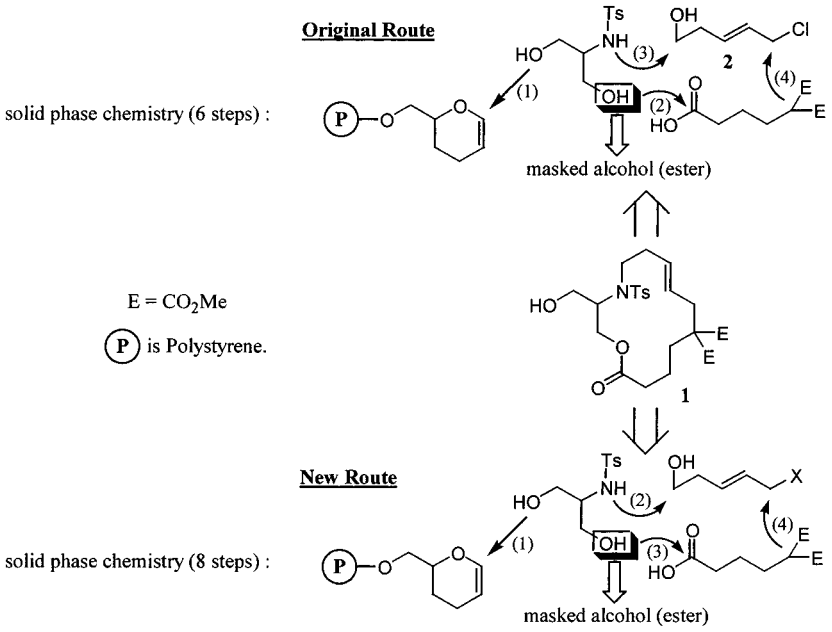
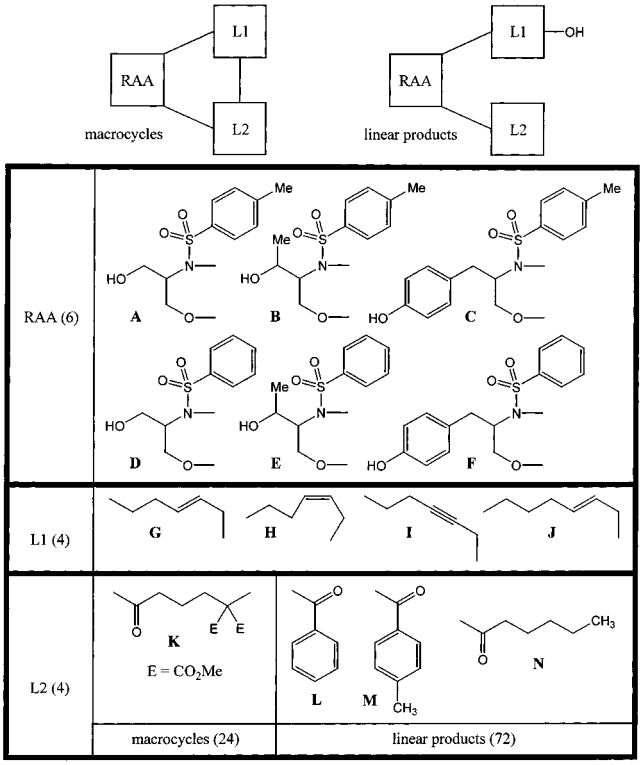
Scheme 1



X is originally a protected alcohol which is transformed into a leaving group prior to macrocyclization.

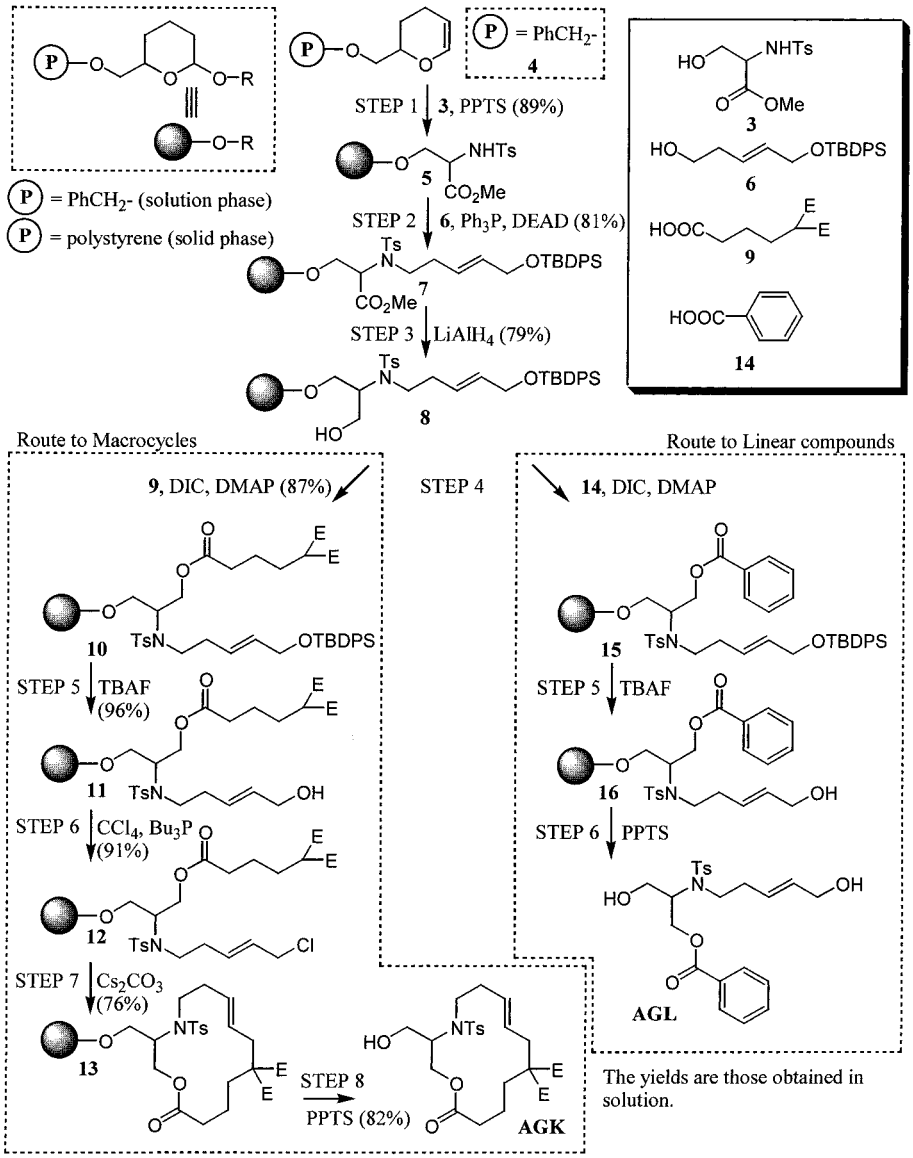
Table 1. Composition of the Library



the previous one[5] (*N*-chlorosuccinamide, triphenylphosphine, imidazole). The macrocyclization precursor **12** was then added to a suspension of cesium carbonate in acetonitrile,[11] and the expected macrocycle **13** was obtained with a yield of 76%. Finally (step 8), the tetrahydropyrannyl ether protecting group was cleaved by means of pyridinium paratoluenesulfonate to release the macrocyclic alcohol **AGK** (82%). Although the route is two steps longer than the former one (Scheme 1),[5] **AGK** was obtained with an overall yield of 27%, which is not much lower than the 35% yield obtained during the six-step sequence procedure. On the other hand, the route is now very robust and more suitable for combinatorial preparation of libraries. The same eight-step sequence was repeated on solid support using the same conditions, and **AGK** was obtained in 28% overall yield.

The eight-step sequence as described above was slightly modified to prepare acyclic compounds. In this series **AGL** was synthesized directly on solid support in six steps (Scheme 2) with an overall yield of 52%. The only difference with the route to macrocycles lies in the fact that the allylic chloride formation and the macrocyclization (steps 6 and 7) are not carried out; apart from that, all other steps are absolutely identical. As a result, a library composed of macrocycles and acyclic compounds can be prepared according to a common scheme (Scheme 3): 96 Kans (IRORI)[12] were loaded with DHP resin and were sorted into six vessels for the first step. Each vessel was treated with PPTS and one of the corresponding six amino acid ester building blocks (Ts-Ser-OMe,[5] Ts-Thr-OMe,[13] Ts-Tyr-OMe,[7] $PhSO_2$-Ser-OMe,[14] $PhSO_2$-Thr-OMe,[15] and $PhSO_2$-Tyr-OMe[16]) (step 1 in Scheme 3). After completion of the reaction (estimated to be 48 h from same experiment carried out in solution), the Kans were pooled together, sorted into four vessels for Mitsunobu coupling with the corresponding alcohol building (HO-**G**-OTBDPS,[5] HO-**H**-OTBDPS,[18] HO-**I**-OTBDPS,[19] and HO-**J**-OTBDPS[20]) (step 2 in Scheme 3). All Kans were pooled together in one reaction flask, and the reduction step 3 with lithium aluminum hydride was accomplished. The Kans were then sorted again into four vessels for the last coupling with the suitable carboxylic acid building blocks (HO-**K**-H,[5] HO-**L**, HO-**M**, and HO-**N**) by means of DIC and DMAP (step 4 in Scheme 3). The Kans were pooled, and the silyl ether was cleaved with TBAF (step 5). Then all 24 Kans possessing the part **K** were pooled in one reaction vessel, and the other 72 Kans were set aside for cleavage. The 24 allylic alcohols were transformed into

Scheme 2



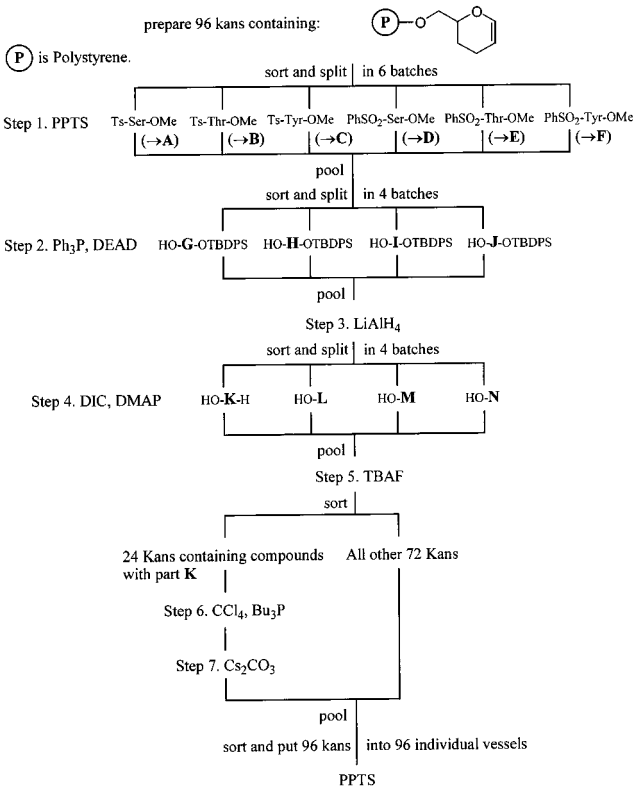
the corresponding allylic chlorides by means of CCl_4 and Bu_3P (step 6) and subsequently macrocyclized with cesium carbonate (step 7). Finally, the 96 Kans were sorted and treated individually with PPTS to yield the final compounds in solution. The 96 reaction mixtures were then evaporated separately and purified by flash chromatography.

The results are summarized in Tables 2 and 3. A total of 59 compounds out of 96 were finally obtained; of which (a) 44 were acyclic compounds with 61% success rate, and (b) 15 were macrocyclic compounds corresponding to 63% success rate.

It can be immediately observed that the propargylic alcohol (HO-**I**-OTBDPS) failed completely, since none of the corresponding 24 final products were ever isolated. To determine at what stage the problem arose, the Mitsunobu reaction with that acetylene linker L1 was tried in solution with tosylamide **5** (polystyrene replaced by benzyl). The tosylamide was fully recovered but the acetylene linker L1 was not found in the reaction mixture. This experiment suggests that our acetylenic linker is not stable under Mitsunobu conditions. If the acetylene L1 linker is removed from the statistics, then 59 of 72 compounds were synthesized which gives the very good success rate of 82%; also 15 of 18 macrocycles were obtained with success rate of 83%. From the detailed analysis of the results (Table 2), it can also be seen that the tyrosine building blocks (leading to **C** and **F** in the final products) were not as efficient as the serine and threonine building blocks (leading to **A**, **B**, **D**, and **E**). This rough observation was confirmed by the lower overall yields obtained with these two building blocks as compared to those obtained with the serine and threonine building blocks. This could be due to the fact that the phenol of tyrosine did not couple as readily to the DHP resin as the alcohols of serine and threonine; and this could lead to a lower loading at step 1. Moreover the THP ether bond (as in tyrosine) is not as stable as the alcohol THP ether bond (as in serine and threonine).

The macrocycles which were formed bear two "unsaturations", one being a formal unsaturation that comes from the building blocks L1, and the other is the ester functionality that provides some restriction in the flexibility of the macrocycles. This number of unsaturations seems almost

Scheme 3



ideal for this range of macrocycle size (14 and 15 members), and as a result all macrocycles derived from serine and threonine were synthesized in similar yields (the tyrosine macrocycles were obtained with lower yields as explained above). The size of the macrocycles controlled by the L1 building blocks HO-**G**-OTBDPS and HO-**J**-OTBDPS and the geometry of the unsaturation controlled by the L1 building blocks HO-**G**-OTBDPS and HO-**H**-OTBDPS did not produce significant effects on the yields that are all within the same range (17−36%). It is not at all clear why the L1 linker HO-**G**-OTBDMS was very successful (it failed only once), whereas HO-**J**-OTBDPS which bears only one additional CH_2 group when compared to HO-**G**-OTBDPS failed to yield the desired product on nine occasions.

Conclusion

The work described in this paper demonstrates that the synthesis of libraries of macrolides and other macroheterocycles is a feasible goal in solid phase combinatorial chemistry. The limitations in terms of number and nature of unsaturations and ring size are now well understood so that the methodology shown here can be considered to be general and is suitable for the preparation of arrays of compounds.

Experimental Section

(a) Solution Phase Chemistry. General. All reactions were performed with continuous stirring under dry argon atmosphere. Commercial reagents were used without further purification. ^{1}H NMR (Varian 300 MHz) spectra were recorded using tetramethylsilane as an internal standard. LCMS was performed using symmetry C8 column with PDA detection from Waters/Micromass. TLC was performed on E. Merck 5715-7 plates. Flash chromatography was carried out using EM Science silica gel 60, 230−400 mesh. Macrocyclization reactions were carried out under high dilution condition using a KD scientific syringe pump. For all experiments in solution phase, the polystyrene polymer had been replaced by a benzyl group.

Preparation of DHP Linker (3,4-Dihydro-2*H*-pyran-2-methanol). A suspension of 3,4-dihydro-2*H*-pyran-2-carboxylic acid salt (5.0 g, 33.3 mmol) in THF (150 mL) was cooled to 0 °C on an ice bath and was treated with LAH (1.3 g, 33.3 mmol) in small portions for over 5 min. After completion of the addition, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. It was then cooled to 0 °C and quenched by slow addition of 1 N NaOH (4 mL). The slurry was diluted with ether (200 mL) and stirred for over 20 min and filtered through Celite. The filtrate was dried over anhydrous Na_2SO_4, and the solvent was evaporated at reduced pressure with the bath temperature not exceeding 15 °C, the product being volatile. The product was directly used for the next step without further purification (3.26 g, 86%). ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 2H), 2.10 (m, 2H), 2.89 (s, 1H), 3.56 (bs, 2H), 3.86 (m, 1H), 4.57 (s, 1H), 6.38 (d, 1H, J = 5.8 Hz). MS (MH^+, 115).

DHP Resin Mimic 4 (Solution Phase Model). A solution of 3,4-dihydro-2*H*-pyran-2-methanol (3.50 g, 30.7 mmol) in 50 mL of DMF was treated with NaH (1.25 g, 31.0 mmol, 60% suspension in oil), and the reaction mixture was stirred at room temperature for over 40 min before adding benzyl chloride (3.6 mL, 31.0 mmol). Stirring was continued at ambient temperature for 12 h and quenched with water. The reaction mixture was diluted with ether (100 mL) and washed with water (3×), and the organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated. The crude compound was purified with flash chromatography (3:1 hexane/ethyl acetate with 1% triethylamine). The desired compound **4** was obtained as a yellow oil (5.2 g, 83%). ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 2H), 2.0 (m, 2H), 2.72 (S, 1H), 3.56 (bs, 2H), 3.84 (m, 1H), 4.52 (s, 2H), 4.70 (bs, 1H), 6.35 (d, 1H, J = 6 Hz), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.46, 24.67, 72.52, 73.42, 74.11, 100.45, 127.17, 127.73, 127.81, 138.27, 143.70. MS (MH^+, 205).

Preparation of 5 (Step 1). To the solution of DHP resin mimic **4** (2.0 g, 9.80 mmol) in 1,2-dichloroethane (30 mL) was added tosyl serine ester **3** (3.0 g, 11 mmol) and pyridinium *p*-toluenesulfonate (1.26 g, 5 mmol), and the reaction mixture was stirred at 65 °C for 14 h. After cooling it to room temperature it was diluted with CH_2Cl_2 (100 mL) and washed with water (2×). The organic layer was separated and dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude compound was purified with flash chromatography (2:1 hexane/ethyl acetate). The desired compound **5** was obtained as a colorless oil (4.2 g, 89%). ^{1}H NMR ($CDCl_3$) δ 1.52−1.80 (m, 6H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40−3.41 (m, 2H), 3.53 (s, 3H), 3.55 (s, 3H), 3.82 (m, 2H), 4.01−4.05 (m, 1H), 4.12−4.16 (m, 1H), 4.53 (s, 2H), 4.60 (s, 2H), 4.71 (s, 1H), 4.74 (s, 1H), 5.48 (d, 1H, J = 9.17 Hz), 5.85 (d, 1H, J = 9.5 Hz), 7.23−7.32 (m, 7H), 7.71 (d, 2H, J = 8.22 Hz). ^{13}C NMR

Table 2. Library Results[a]

Library 96

RAA	L1				L2
↓	G	H	I	J	↓
A	27% - 512	22% - 512	0%	32% - 526	K (mac)
	50% - 451*	35% - 451*	0%	45% - 448	L
	48% - 448	48% - 448	0%	43% - 462	M
	27% - 445*	50% - 445*	0%	42% - 464**	N
B	36% - 526	17% - 526	0%	30% - 540	K (mac)
	30% - 448	31% - 448	0%	25% - 462	L
	20% - 462	33% - 462	0%	25% - 476	M
	34% - 464**	38% - 464**	0%	0%	N
C	0%	0%	0%	0%	K (mac)
	10% - 532**	10% - 532**	0%	0%	L
	10% - 547**	6% - 547**	0%	0%	M
	27% - 504	10% - 504	0%	0%	N
D	36% - 498	17% - 498	0%	25% - 512	K (mac)
	24% - 420	44% - 420	0%	42% - 434	L
	36% - 434	31% - 434	0%	0%	M
	40% - 414	36% - 414	0%	0%	N
E	33% - 512	20% - 512	0%	27% - 526	K (mac)
	42% - 434	27% - 434	0%	37% - 448	L
	34% - 448	0%	0%	33% - 462	M
	62% - 450**	40% - 450**	0%	34% - 464**	N
F	13% - 574	17% - 574	0%	17% - 588	K (mac)
	10% - 518**	27% - 518	0%	0%	L
	7% - 532**	0%	0%	0%	M
	31% - 490	10% - 490	0%	30% - 504	N

[a] Total yields and mass spectrometry data ($[MH]^+$) are indicated. *: $[MNH_4]^+$. **: $[MNa]^+$.

Table 3. Detailed Analysis of the Results (per Building Blocks)

RAA						L1				L2			
A (ser)	B (ser)	C (tyr)	D (ser)	E (ser)	F (tyr)	G	H	I	J	K	L	M	N
12	11	6	10	11	9	23	21	0	15	15 macrocycles	16	13	15
Over 16						Over 24							

($CDCl_3$) δ 17.56, 21.52, 27.10, 27.30, 29.15, 29.41, 30.53, 30.75, 52.51, 55.85, 56.77, 67.25, 68.39, 68.47, 68.94, 72.74, 73.09, 73.28, 73.31, 75.10, 97.37, 98.34, 102.50, 127.12, 127.27, 127.51, 129.33, 129.45, 129.56, 138.37, 143.45, 169.87, 170.03. MS (MH^+, 478).

Preparation of 7 (Step 2). To a solution of **5** (2.0 g, 4.19 mmol) in THF (20 mL) were added **6** (2.12 g, 6.3 mmol) and PPh_3 (1.65 g, 6.3 mmol). The reaction mixture was cooled to 0 °C on an ice bath, and DEAD (1.0 mL, 6.3 mmol) was added to it. The reaction mixture was stirred at this temperature for 20 min and at room temperature for 7 h. The solvent was evaporated, and the residue was purified by flash chromatography (7:3 toluene/diethyl ether). The desired compound **7** was isolated as a yellow oil (2.71 g, 81%). ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.51−1.65 (m, 6H), 2.35 (m, 2H), 2.39 (s, 3H), 3.24−3.27 (m, 2H), 3.37−3.39 (m, 2H), 3.46 (m, 2H), 3.55 (s, 3H), 3.58 (s, 3H), 3.78 (m, 2H), 4.10 (bs, 2H), 4.13 (m, 1H), 4.55 (s, 2H), 4.57 (s, 2H), 4.76 (s, 1H), 4.86 (s, 1H), 5.55 (m, 2H), 7.32−7.39 (m, 14H), 7.64−7.72 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 17.60, 21.48, 26.79, 27.30, 29.25, 30.80, 33.26, 33.71, 46.46, 46.58, 52.15, 59.20, 59.92, 64.26, 65.93, 66.19, 68.48, 73.24, 75.38, 97.25, 98.21,

126.67, 127.47, 127.58, 128.31, 129.33, 129.60, 131.10, 133.68, 129.33, 129.60, 131.10, 133.68, 135.48, 143.19, 169.58. MS (MH^+, 800).

Preparation of 8 (Step 3). To a solution of **7** (2.6 g, 3.25 mmol) in THF (30 mL) cooled to 0 °C on a ice bath was added 1.0 M LAH (9.75 mL, 9.75 mmol). The reaction mixture was stirred at this temperature for 30 min and at room temperature for 3 h. It was then cooled to 0 °C and quenched with saturated aqueous NH_4Cl. Ether (60 mL) was added, and the organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated off. The residue was purified using flash chromatography (1:1 hexane/ethyl acetate) to give **8** as a colorless oil (1.98 g, 79%). ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.50−1.59 (m, 6H), 2.38 (s, 3H), 2.39 (m, 2H), 3.24 (m, 2H), 3.35−3.42 (m, 4H), 3.75 (m, 2H), 3.96 (m, 1H), 4.11 (bs, 3H), 4.53 (s, 2H), 4.64 (s, 1H), 4.72 (s, 1H), 5.57 (m, 2H), 7.29−7.40 (m, 14H), 7.64−7.75 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 17.63, 19.15, 21.43, 26.76, 27.05, 29.12, 29.25, 33.84, 33.97, 45.03, 45.23, 59.17, 59.59, 61.40, 62.11, 64.19, 65.11, 66.06, 66.57, 68.51, 68.72, 73.11, 73.24, 97.56, 126.57, 126.88, 127.14, 127.58, 128.30, 129.53, 131.27, 131.40, 135.46. MS (MH^+, 772).

Preparation of 10 (Step 4). To a solution of **8** (1.72 g, 2.23 mmol) in CH_2Cl_2 (15 mL) were added **9** (730 mg, 3.35 mmol), DIC (0.53 mL, 3.35 mmol), and DMAP (110 mg, 0.90 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated off, and the residue was purified by flash chromatography (2:1 hexane/ethyl acetate) to give **10** as a colorless oil (1.87 g, 87%). ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.51−1.56 (m, 8H), 1.82 (m, 2H), 2.12 (t, 2H, J = 7.5 Hz), 2.39 (m, 5H), 3.24 (m, 2H), 3.36−3.49 (m, 5H), 3.73 (s, 7 H), 3.92 (m, 1H), 4.10 (bs, 2H), 4.50 (bs, 2H), 4.59 (s, 1H), 4.61 (s, 1H), 5.58 (m, 2H), 7.25−7.42 (m, 14H), 7.61−7.69 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 17.59, 19.15, 21.45, 22.68, 26.75, 27.15, 28.42, 29.12, 29.15, 33.76, 33.85, 34.11, 45.14, 45.30, 51.66, 52.90, 59.17, 59.71, 61.39, 63.23, 65.46, 67.63, 68.72, 72.93, 73.01, 98.61, 127.13, 127.27, 127.68, 128.13, 129.56, 134.40, 135.41, 169.64, 178.83. MS (MH^+, 972).

Preparation of 11 (Step 5). To a solution of **10** (1.66 g, 1.70 mmol) in THF (10 mL) was added a 1.0 M solution of TBAF (2.7 mL, 2.7 mmol), and the reaction mixture was stirred for 3 h at room temperature. Ether (30 mL) was then added to the reaction mixture, and it was washed with a saturated solution of aqueous NH_4Cl (2×), the organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was then purified by flash chromatography (1:1 hexane/ethyl acetate) to furnish **11** as an oily compound (1.19 g, 96%). ^1H NMR ($CDCl_3$) δ 1.53−1.60 (m, 8 H), 1.83 (m, 2H), 2.14 (m, 2H), 2.14 (m, 2H), 2.37 (m, 5H), 3.19 (m, 2H), 3.39−3.41 (m, 5H), 3.72 (s, 7H), 3.91 (m, 1H), 4.16 (s, 1H), 4.53 (s, 2H), 4.58 (s, 1H), 4.61 (s, 1H), 5.60 (m, 2H), 7.23−7.32 (m, 7H), 7.69 (d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ 17.60, 21.42, 22.32, 27.17, 27.29, 29.12, 29.30, 33.33, 33.51, 44.39, 44.85, 51.30, 52.54, 56.03, 56.36, 62.13, 62.44, 65.98, 67.16, 68.56, 73.25, 75.38, 97.62, 102.17, 127.20, 127.50, 128.30, 129.52, 131.47, 137.96, 169.51, 172.42. MS (MH^+, 734).

Preparation of 12 (Step 6). A solution of **11** (1.10 g, 1.51 mmol) in CCl_4 (10 mL) was cooled to 0 °C on an ice bath, and tributylphosphine (1.1 mL, 4.53 mmol) was slowly added to it. After complete addition, the reaction mixture was stirred at this temperature for over 20 min and at room temperature for 1 h. The solvent was evaporated off, and the residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to furnish the desired compound **12** (1.03 mg, 91%). ^1H NMR ($CDCl_3$) δ 1.54−1.59 (m, 8H), 1.85 (m, 2H), 2.27 (t, 2H, J = 7.6 Hz), 2.38 (m, 5H), 3.25 (m, 2H), 3.34−3.40 (m, 5H), 3.72 (s, 7H), 3.84 (m, 1H), 3.95 (d, 2H, J = 5.0 Hz), 4.53 (s, 2H), 4.68 (s, 1H), 4.74 (s, 1H), 5.61 (m, 2H), 7.23−7.31 (m, 7H), 7.69 (d, 2H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 17.60, 21.43, 22.31, 27.17, 27.30, 28.08, 29.12, 30.79, 33.34, 33.56, 44.85, 52.56, 62.45, 65.98, 73.25, 102.17, 127.20, 127.50, 129.52, 131.47, 138.27, 143.18, 169.57, 173.42. MS (MH^+, 752).

Preparation of 13 (Step 7). A suspension of Cs_2CO_3 (186 mg, 0.57 mmol) in acetonitrile (50 mL) was heated to 70 °C on an oil bath. The substrate **12** (43 mg, 0.057 mmol) was dissolved in acetonitrile (1.0 mL) and was slowly added to the above suspension via syringe pump for 10 h (1.1×10^{-3} M concentration after addition). After complete addition, the reaction mixture was stirred at this temperature for a further 3 h and then cooled to room temperature. The solvent was evaporated off; the residue was diluted with ether (30 mL), washed (2×) with water, and dried over anhydrous Na_2SO_4; and the solvent was removed under reduced pressure. The crude was flash chromatographed (1:1 hexane/ethyl acetate) to furnish the desired macrocycle **13** (31 mg, 76%). ^1H NMR ($CDCl_3$) δ 1.39−1.56 (m, 8H), 1.91 (m, 2H), 2.24−2.29 (m, 2H), 2.35 (m, 5H), 2.64 (t, 2H, J = 7.2 Hz), 3.28 (m, 2H), 3.37 (m, 2H), 3.48 (m, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 4.06 (t, 1H, J = 10.35 Hz), 4.19 (m, 1H), 4.34 (s, 1H), 4.36 (s, 1H), 4.53 (s, 2H), 4.54 (s, 1H), 4.67 (s, 1H), 5.21 (m, 2H), 5.53 (m, 2H), 7.18−7.27 (m, 7H), 7.68 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ 17.41, 19.50, 21.19, 21.42, 22.32, 27.27, 28.09, 29.42, 31.26, 32.89, 33.45, 34.50, 35.36, 44.62, 52.64, 52.99, 56.36, 62.44, 63.15, 67.18, 68.58, 102.24, 127.56, 128.42, 129.61, 131.47, 137.84, 143.74, 169.32, 172.46. MS (MH^+, 716).

Preparation of AGK (Step 8). To a solution of **13** (28 mg, 0.039 mmol) in 1,2-dichloroethane (6 mL) and methanol (14 mL) was added pyridinium *p*-toluenesulfonate (39 mg, 0.16 mmol), and the reaction mixture was stirred at 70 °C for 12 h. It was then cooled to room temperature, and the solvent was evaporated. The residue was then diluted with ether (20 mL) and washed with water (2×). The organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified using flash chromatography (1:1 hexane/ethyl acetate) to give the desired macrocycle **AGK** as colorless oil (16.4 g, 82%). ^1H NMR ($CDCl_3$) δ 1.44 (m, 2H), 1.85 (m, 2H), 2.26 (m, 4H), 2.42 (s, 3H), 2.59 (m, 2H), 3.30 (m, 1H), 3.56 (m, 1H), 3.66 (m, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 4.11 (m, 1H), 4.21 (m, 2H), 5.16 (m, 1H), 5.45 (m, 1H), 7.30 (d, 2H, J = 7.96 Hz), 7.72 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ 19.46, 21.91, 31.18, 32.71, 34.64, 35.28, 45.31, 52.90, 52.99, 56.70, 59.53, 61.09, 63.12, 126.05,

127.57, 129.94, 132.52, 137.64, 143.74, 171.63, 171.76, 171.95. MS (MH^+, 512).

(b) Solid Phase Chemistry. General. The solid phase was carried out with Unisphere 200 Merrifield HL resin (with a loading of 1.21 mmol Cl/g, 1% DVB, 70−90 mesh) purchased from Irori. The chemistry was carried out in macroKans, and radio frequency tags were used as a coding device. Sorting was done manually.

Preparation of a Batch of DHP Resin (10 g). A solution of 3,4-dihydro-2*H*-pyran-2-methanol (7.0 g, 61 mmol) in DMF (70 mL) at room temperature was treated with NaH (2.5 g 62 mmol, 60% suspension in oil). After complete addition the reaction mixture was stirred at this temperature for 40 min. Then Merrifield resin (10 g, 12.1 mmol, 1.21 mmol Cl/g) was added to it. The mixture was then left to shake on a platform shaker (at 200 rpm) for 18 h at room temperature. The suspension was reddish brown and was quenched with water (4 mL), and the solvent was filtered off under suction using a sintered funnel. The resin was washed several times with DMF, DCM (2 × 30 mL), MeOH (5 × 30 mL), and DCM (10 × 50 mL) and dried at high vacuum for over 48 h to give the desired product (10.13 g). This batch was later used for optimization studies in the Kans and subsequently for the library synthesis.

Typical Procedure (Preparation of AGK and AGL, See Scheme 2). The amounts of equivalents of building blocks needed are calculated on the basis of original loading of Merrifield resin (1.21 mmol Cl/g).

Preparation of 5 (Step 1). Four macroKans filled with DHP resin (100 mg) were put into a 250 mL round-bottom flask, and about 60 mL of 1,2-dichloromethane was added to it. This was followed by addition of amino acid building block **3** (655 mg, 2.4 mmol, 5 equiv) and pyridinium *p*-toluenesulfonate (542 mg, 2.16 mmol, 4.5 equiv). The Kans were then stirred at 70 °C for 48 h. After cooling the flask to room temperature, the solvent was sucked out under vacuum (water pump) and the Kans were washed with the following solvents: DMF (4 × 100 mL), water (3 × 100 mL), DMF (6 × 100 mL), MeOH (5 × 100 mL), and CH_2Cl_2 (6 × 100 mL) and dried by means of a high vacuum pump for 12 h.

Preparation of 7 (Step 2). THF (40 mL) was added to the above flask containing the four Kans, and the mixture was cooled to 0 °C on an ice bath. Building block **6** (816 mg, 2.4 mmol, 5 equiv) was added, then triphenyl phosphine (629 mg, 2.4 mmol, 5 equiv), and diethyl azodicarboxylate (38 mL, 2.4 mmol, 5 equiv). Stirring was continued for 20 min at this temperature and then at room temperature for 12 h. The solvent was then sucked out under vacuum, and the Kans were washed with the following solvents: CH_2Cl_2 (3 × 100 mL), DMF/ether (1:1) (4 × 100 mL), and CH_2Cl_2 (5 × 100 mL) and dried under high vacuum.

Preparation of 8 (Step 3). THF (40 mL) was added to the above flask, and the mixture was cooled to 0 °C on an ice bath. A solution of 1.0 M LAH (1.92 mL, 1.92 mmol, 4 equiv) was subsequently added, and stirring was continued at this temperature for 30 min. It was then stirred at room temperature for 3 h, the solvent was sucked under vacuum, and the Kans were quenched with ethyl acetate (100 mL). This was followed by the following washings: 0.1 N aqueous NaOH (40 mL), and water (5 × 100 mL). The Kans were then stirred with saturated aqueous NH_4Cl for 4 h and further washed with the following solvents: water (5 × 100 mL), DMF (6 × 100 mL), MeOH (5 × 100 mL), THF (3 × 100 mL), and CH_2Cl_2 (5 × 100 mL) and dried under high vacuum for 24 h.

Preparation of 10 and 15 (Step 4). To prepare **10**, two macroKans were sorted out and put into a 250 mL round-bottom flask, and CH_2Cl_2 (20 mL) was added to it. This was followed by addition of building block **9** (262 mg, 1.2 mmol, 5.0 equiv), DIC (0.19 mL, 1.2 mmol, 5.0 equiv), and DMAP (59 mg, 0.48 mmol, 2.0 equiv). The Kans were stirred at room temperature for 10 h and washed with the following solvents: THF (3 × 50 mL) and CH_2Cl_2 (6 × 30 mL). The Kans were then dried under high vacuum for 12 h.

The two remaining Kans were used to prepare **15**. They were put into a 250 mL round-bottom flask, and CH_2Cl_2 (20 mL) was added to it. This was followed by addition of building block **14** (293 mg, 2.4 mmol, 10 equiv), DIC (0.38 mL, 2.4 mmol, 10 equiv), and DMAP (117 mg, 0.96 mmol, 4 equiv). The Kans were stirred at room temperature for 10 h and washed with the following solvents: THF (3 × 50 mL) and CH_2Cl_2 (6 × 30 mL). The Kans were then dried under high vacuum for 12 h. Excess equivalents of reagents were used in the latter case because benzoic acid **14** (and also toluic and hexanoic acids, see building blocks L2 HO-**M** and HO-**N**) was commercially available and was therefore less valuable than **9**.

Preparation of 11 and 16 (Step 5). The four Kans were pooled into a 250 mL round-bottom flask. THF (40 mL) was added followed by TBAF (2.4 mL, 2.4 mmol, 5.0 equiv), and the resulting mixture was stirred at room temperature for 3 h. The Kans were then washed with the following solvents: saturated aqueous NH_4Cl (3 × 100 mL), water (5 × 100 mL), DMF (6 × 100 mL), MeOH (6 × 100 mL), THF (6 × 100 mL), and CH_2Cl_2 (6 × 100 mL) and finally dried under high vacuum.

Preparation of 12 (Step 6). The two Kans containing **11** were sorted and put into a 100 mL round-bottom flask for the chlorination step. CCl_4 (20 mL) was added, and the reaction mixture was cooled to 0 °C on an ice bath. Tributylphosphine (0.60 mL, 2.4 mmol, 10 equiv) was then added, and the Kans were stirred at this temperature for 20 min and at room temperature for 4 h. The Kans were then washed with the following solvents: CH_2Cl_2 (5 × 50 mL), THF/MeOH (1:1) (5 × 50 mL), and CH_2Cl_2 (6 × 50 mL) and dried under high vacuum.

Preparation of 13 (Step 7). To the 100 mL round-bottom flask containing the two Kans filled with **12** were added acetonitrile (60 mL) and Cs_2CO_3 (1.9 g, 6 mmol, 25 equiv). The mixture was stirred at 70 °C on a oil bath for 24 h. The Kans were then cooled to room temperature and washed with the following solvents: DMF (2 × 100 mL), H_2O (3 × 100 mL), DMF (4 × 100 mL), MeOH (4 × 100 mL), CH_2Cl_2 (5 × 100 mL) and dried under high vacuum.

Preparation of AGK (Step 8). To the two Kans in the 100 mL round-bottom flask was added pyridinium *p*-toluenesulfonate (602 mg, 2.4 mmol, 10 equiv) in 1,2-

dichloroethane (6 mL) and methanol (14 mL), and the reaction mixture was stirred at 70 °C for 12 h. It was then cooled to room temperature, and solvents were evaporated off. The residue was diluted with CH_2Cl_2 (15 mL) and the Kans were washed several times with portions of CH_2Cl_2 (5 mL). The organic layer was combined and washed with H_2O (1×), separated, and dried over anhydrous Na_2SO_4, and the solvent was rotovaporated. The crude compound was then purified using flash chromatography (1:1 hexane/ethyl acetate), and the desired compound was isolated as a white oil (29 mg, 28% overall yield). All the spectral data were identical to that of the authentic sample (synthesized in solution phase) as described above.

Preparation of AGL (Step 6). The experimental details are the same as described above for **AGK**. The desired compound was isolated as a white oil (54 mg, 52% overall yield). ^{1}H NMR ($CDCl_3$) δ 2.42 (bs, 5H), 3.35 (m, 2H), 3.65 (dd, 2H, J = 4.39 Hz, 11.26 Hz), 3.72 (dd, 2H, J = 3.84 Hz, 10.98 Hz), 4.26 (d, 2H, J = 4.94 Hz), 5.79 (m, 2H), 7.26 (d, 2H, J = 10.98 Hz), 7.44 (m, 2H), 7.61 (m, 1H), 7.76 (d, 2H, J = 8.24 Hz), 8.07 (d, 2H, J = 8.51 Hz). ^{13}C NMR ($CDCl_3$) δ 21.92, 50.54, 55.56, 58.99, 63.88, 100.39, 127.65, 130.02, 130.34, 131.26, 133.82. MS (MNN_4+, 451).

(c) Solid Phase Combinatorial Synthesis of the Library. General. The library of acyclic as well as macrocyclic products was carried out according to Scheme 3 and used the Irori technology with Unisphere 200 Merrifield HL resin (with a loading of 1.21 mmol Cl/g, 1% DVB, 70−90 mesh). MacroKans (containing 100 mg of DHP linker bound resin) were used for making the library of macrocycles, while miniKans (containing 50 mg of DHP linker bound resin) were used for making the library of acyclic compounds. Radio frequency tags were used as a coding device, and sorting was done manually. The cleavage was carried out on 96 individual 100 mL round-bottom flasks each containing a single Kan according to the procedures described above for compounds **AGK** and **AGL**. The final products were purified using flash chromatography with suitable solvent system and characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

Spectral data for macrocycles: **AHK:** ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H), 1.85 (m, 2H), 2.28 (m, 4H), 2.42 (s, 3H), 2.59 (m, 2H), 3.29 (m, 1H), 3.56 (m, 1H), 3.68 (m, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 4.18 (m, 1H), 4.20 (m, 2H), 5.16 (m, 1H), 5.43 (m, 1H), 7.30 (d, 2H, J = 7.96 Hz), 7.72 (d, 2H, J = 8.24 Hz). ^{13}C NMR ($CDCl_3$) δ 19.46, 21.91, 31.18, 32.70, 34.64, 35.28, 45.30, 52.90, 52.99, 56.70, 59.52, 61.09, 63.12, 126.05, 127.57, 129.94, 132.51, 137.64, 143.74, 171.39, 171.76, 172.96. MS (MH^+, 512).

AJK: ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2H), 1.69 (m, 4H), 2.11 (m, 2H), 2.25 (m, 2H), 2.41 (m, 3H), 2.55 (m, 2H), 3.19 (m, 2H), 3.69 (m, 2H), 3.56 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 3.86 (m, 1H), 3.95 (m, 1H), 4.34 (m, 1H), 5.19 (m, 1H), 5.23 (m, 1H), 7.30 (d, 2H, J = 7.96 Hz), 7.72 (d, 2H, J = 8.20 Hz). ^{13}C NMR ($CDCl_3$) δ 13.96, 19.96, 21.89, 24.58, 24.63, 30.23, 30.36, 32.20, 35.18, 36.48, 46.42, 52.94, 56.94, 59.04, 61.50, 64.24, 125.75, 127.28, 130.08, 134.27, 137.49, 143.74, 171.54, 171.62, 172.88. MS (MH^+, 526).

BGK: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 6.3 Hz), 1.40 (m, 2H), 1.71 (m, 2H), 2.24 (m, 4H), 2.43 (s, 3H), 2.56 (m, 2H), 3.36 (m, 1H), 3.69 (m, 4H), 3.71 (m, 3H), 3.95 (m, 1H), 4.08 (m, 1H), 4.14 (m, 2H), 5.10 (m, 1H), 5.40 (m, 1H), 7.33 (d, 2H, J = 7.97 Hz), 7.74 (d, 2H, J = 8.24 Hz). ^{13}C NMR ($CDCl_3$) δ 19.28, 21.82, 21.90, 31.20, 32.39, 34.66, 35.22, 52.89, 52.94, 56.58, 125.75, 127.64, 129.94, 132.62, 137.88, 143.79, 171.62, 172.62. MS (MH^+, 526).

BHK: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 6.86 Hz), 1.73 (m, 4H), 2.25 (m, 4H), 2.59 (s, 3H), 2.61 (d, 2H, J = 7.69 Hz), 3.35 (m, 1H), 3.46 (m, 1H), 3.71 (bs, 4H), 3.92 (m, 2H), 4.21 (m, 1H), 5.08 (m, 1H), 5.40 (m, 1H), 7.30 (d, 2H, J = 7.96 Hz), 7.73 (d, 2H, J = 8.21 Hz). ^{13}C NMR ($CDCl_3$) δ 20.26, 21.35, 21.89, 28.96, 30.55, 31.57, 35.03, 45.84, 52.93, 52.96, 57.03, 63.48, 64.20, 65.96, 125.06, 127.35, 130.03, 130.40, 137.86, 143.90, 171.38, 171.41, 171.87. MS (MH^+, 526).

BJK: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 7.1 Hz), 1.42 (m, 2H), 1.72 (m, 4H), 2.22 (m, 4H), 2.43 (s, 3H), 2.54 (m, 2H), 3.16 (m, 2H), 3.67 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.95 (m, 1H), 4.21 (m, 1H), 5.18 (m, 1H), 5.45 (m, 1H), 7.35 (d, 2H, J = 7.41 Hz), 7.70 (d, 2H, J = 8.24 Hz). ^{13}C NMR ($CDCl_3$) δ 19.85, 20.22, 21.94, 30.05, 30.27, 30.45, 32.12, 35.23, 36.41, 46.70, 52.97, 57.00, 64.06, 65.81, 125.72, 127.41, 130.22, 134.12, 137.10, 144.01, 171.52, 171.60, 172.21. MS (MH^+, 540).

DGK: ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2H), 1.81 (m, 2H), 2.27 (m, 4H), 2.58 (m, 2H), 3.31 (m, 1H), 3.53 (m, 1H), 3.65 (m, 2H), 3.69 (s, 3h), 3.71 (s, 3H), 4.02 (m, 1H), 4.23 (m, 2H), 5.28 (m, 1H), 5.47 (m, 1H), 7.52 (m, 3H), 7.84 (d, 2H, J = 8.24 Hz). ^{13}C NMR ($CDCl_3$) δ 19.44, 31.17, 32.63, 34.61, 35.25, 45.26, 52.90, 53.00, 56.69, 59.47, 61.05, 63.00, 126.14, 127.53, 129.33, 132.42, 132.89, 140.60, 171.62, 171.77, 172.95. MS (MH^+, 498).

DHK: ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 2H), 1.75 (m,2H), 2.29 (m, 4H), 2.64 (d, 2H, J = 7.69 Hz), 3.31 (m, 1H), 3.44 (m, 1H), 3.69 (m, 2H), 3.72 (s, 6H), 4.05 (m, 2H), 4.41 (m, 1H), 5.13 (m, 1H), 5.42 (m, 1H), 7.52 (m, 2H), 7.84 (d, 2H, J = 7.96 Hz). ^{13}C NMR ($CDCl_3$) δ 20.62, 24.66, 29.53, 30.90, 32.03, 35.07, 45.52, 52.97, 53.00, 56.99, 58.70, 60.84, 64.11, 125.09, 127.22, 127.55, 129.33, 129.47, 130.19, 133.02, 140.59, 171.38, 171.44, 172.74. MS (MH^+, 498).

DJK: ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2H), 1.70 (m, 4H), 2.08 (m, 2H), 2.21 (m, 2H), 2.54 (m, 2H), 3.14 (m, 1H), 3.21 (m, 1H), 3.70 (m, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 3.97 (m, 2H), 4.36 (m, 1H), 5.14 (m, 1H), 5.42 (m, 1H), 7.60 (m, 3H), 7.87 (d, 2H, J = 7.96 Hz). ^{13}C NMR ($CDCl_3$) δ 20.00, 30.22, 30.26, 35.08, 36.53, 46.60, 52.94, 56.93, 59.18, 61.68, 64.07, 125.85, 127.27, 129.50, 132.94, 134.23, 140.44, 171.54, 171.59, 172.95. MS (MH^+, 512).

EGK: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 6.31 Hz), 1.40 (m, 2H), 1.60 (m, 2H), 2.26 (m, 4H), 2.55 (s, 3H), 2.57 (m, 2H), 3.34 (m, 1H), 3.69 (bs, 4H), 3.70 (s, 3H), 3.92 (m, 1H), 4.18 (m, 2H), 5.17 (m, 1H), 5.35 (m, 1H), 7.57 (m, 3H), 7.86 (d, 2H, J = 7.96 Hz). ^{13}C NMR ($CDCl_3$) δ 19.29, 21.94, 24.89, 31.23, 32.37, 33.10, 34.63, 35.23, 52.90, 52.96, 56.58, 63.41, 66.65, 125.88, 127.63, 129.33, 132.54, 132.91, 140.87, 171.58, 171.64, 172.62. MS (MH^+, 512).

EHK: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 6.0 Hz), 1.44 (m, 2H), 1.73 (m, 2H), 2.25 (m, 4H), 2.62 (m, 2H), 3.36 (m, 1H), 3.54 (m, 1H), 3.71 (s, 6H), 3.76 (m, 2H), 4.12 (m,

2H), 4.20 (m, 1H), 5.09 (m, 1H), 5.42 (m, 1H), 7.55 (m, 3H), 7.86 (d, 2H, $J = 7.96$ Hz). ^{13}C NMR ($CDCl_3$) δ 20.32, 21.42, 24.60, 24.66, 24.89, 28.93, 30.04, 30.56, 31.57, 35.00, 45.90, 52.95, 57.04, 63.54, 64.14, 65.96, 125.14, 127.33, 127.62, 129.34, 129.42, 130.33, 133.62, 140.84, 171.40, 171.85. MS (MH^+, 512).

EJK: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3H, $J = 6.30$ Hz), 1.37 (m, 2H), 1.75 (m, 4H), 2.16 (m, 4H), 2.53 (m, 2H), 3.14 (m, 2H), 3.69 (m, 2H), 3.71 (bs, 6H), 3.97 (m, 1H), 4.22 (m, 1H), 5.12 (m, 1H), 5.41 (m, 1H), 7.60 (m, 3H), 7.83 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 19.91, 20.34, 21.41, 30.06, 30.47, 32.20, 35.10, 36.50, 46.01, 52.94, 56.97, 60.68, 63.84, 65.97, 125.78, 127.41, 129.57, 133.10, 134.07, 140.10, 171.50, 172.27. MS (MH^+, 526).

FGK: ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H), 1.87 (m, 2H), 2.21 (m, 2H), 2.61 (m, 4H), 3.27 (m, 2H), 3.58 (m, 2H), 3.70 (s, 3H), 3.73 (s, 3H), 3.95 (m, 1H), 4.12 (m, 2H), 5.19 (m, 1H), 5.44 (m, 1H), 6.71 (d, 2H, $J = 8.51$ Hz), 6.93 (d, 2H, $J = 8.51$ Hz), 7.55 (m, 3H), 7.87 (d, 2H, $J = 8.21$ Hz). ^{13}C NMR ($CDCl_3$) δ 19.31, 24.67, 31.07, 32.33, 34.67, 35.28, 35.34, 37.54, 44.02, 52.85, 52.94, 56.70, 59.28, 63.45, 115.88, 126.28, 127.59, 129.01, 129.30, 130.19, 131.85, 132.77, 140.68, 154.91, 171.67, 172.85. MS (MH^+, 574).

FHK: ^{1}H NMR ($CDCl_3$) δ 1.47 (m, 2H), 1.86 (m, 2H), 2.29 (m, 2H), 2.65 (m, 4H), 3.27 (m, 2H), 3.46 (m, 2H), 3.72 (s, 6H), 3.95 (m, 1H), 4.27 (m, 2H), 5.14 (m, 1H), 5.43 (m, 1H), 6.72 (d, 2H, $J = 8.50$ Hz), 6.90 (d, 2H, $J = 8.51$ Hz), 7.25 (m, 3H), 7.81 (d, 2H, $J = 6.90$ Hz). ^{13}C NMR ($CDCl_3$) δ 20.46, 22.91, 29.45, 30.04, 34.65, 37.56, 45.14, 52.95, 56.82, 59.02, 64.81, 66.17, 115.87, 127.26, 129.35, 130.25, 131.07, 132.80, 154.78, 171.26, 172.35. MS (MH^+, 574).

FJK: ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2H), 1.90 (m, 4H), 2.21 (m, 2H), 2.55 (dd, 2H, $J = 4.40$ Hz, 13.71 Hz), 2.81 (dd, 2H, $J = 3.84$ Hz, 14.01 Hz), 3.25 (m, 2H), 3.66 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 3.96 (m, 1H), 4.28 (m, 2H), 4.98 (m, 1H), 5.21 (m, 1H), 6.72 (m, 2H), 6.91 (m, 2H), 7.52 (m, 3H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 20.55, 22.85, 24.10, 24.68, 25.50, 32.00, 33.82, 36.07, 51.61, 52.90, 53.08, 55.64, 62.61, 64.80, 115.86, 126.73, 127.41, 129.08, 129.36, 130.14, 131.64, 132.67, 138.25, 171.29, 172.63. MS (MH^+, 588).

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References and Notes

(1) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648.
(2) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
(3) Xiao, X. Y.; Parandoosh, Z.; Nova, M. P. *J. Org. Chem.* **1997**, *62*, 6029.
(4) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z., Li, T.; Glannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268.
(5) Ramaseshan, M.; Ellingboe, J. W.; Dory, Y. L.; Deslongchamps, P. *Tetrahedron Lett.* In press.
(6) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.
(7) Ramaseshan, M.; Robitaille, M.; Ellingboe, J. W.; Dory, Y. L.; Deslongchamps, P. *Tetrahedron Lett.* In press
(8) Mitsunobu, O. *Synthesis* **1981**, 1.
(9) Gargipati, R. S.; Adams, B.; Adams, J. L.; Sankar, S. K. *J. Org. Chem.* **1996**, *61*, 2911.
(10) Tsutsumi, H.; Ishido, Y. *Carbohydr. Res.* **1982**, *111*, 75.
(11) Brillon, D.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 1131.
(12) Nicolaou, K. C.; Xiao, X. Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2289.
(13) Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069.
(14) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113.
(15) Szechner, B.; Achmatowicz, O.; Galdecki, Z.; Fruzinski, A. *Tetrahedron* **1994**, *50*, 7611.
(16) *N*-Benzenesulfonyl-tyrosine (46 g; 143 mmol) (ref 17) was dissolved in methanol (600 mL), and HCl gas was bubbled through the resulting solution at 0 °C for 40 min. The mixture was stirred at room temperature for 2 h, and the solvent was removed under reduced pressure. The residue was dissolved into ethyl acetate, and the organic solution was washed twice with water and dried ($MgSO_4$). The solvent was removed, and the residue was purified by flash chromatography (2:1 to 1.5:1 hexane/ethyl acetate) to yield the desired compound *N*-benzenesulfonyl-tyrosine methyl ester (47 g, 98%). ^{1}H NMR δ($CDCl_3$): 2.97 (2H, d, $J = 6$ Hz, C*H*$_2$); 3.47 (3H, s, C*H*$_3$); 4.17 (1H, dt, $J = 9$ and 6 Hz, C*H*); 5.03 (1H, d, $J = 9$ Hz, N*H*); 6.70 and 6.93 (4H, AB, $J = 8.5$ Hz, *Ph* Tyr); 7.45 (2H, m, *Ph*SO_2); 7.55 (1H, m, *Ph*SO_2); 7.76 (2H, d, $J = 8.5$ Hz, *Ph*SO_2). ^{13}C NMR δ($CDCl_3$): 38.87, 52.75, 57.06, 115.69, 126.98, 127.30, 129.20, 130.79, 132.97, 139.68, 154.99, 171.34.
(17) Defauw, J. M.; Murphy, M. M.; Jagdmann, G. E.; Hu, H.; Lampe, J. W.; Hollingshead, S. P.; Mitchell, T. J.; Crane, H. M.; Heerding, J. M.; Mendoza, J. S.; Davis, J. E.; Darges, J. W.; Hubbard, F. R.; Hall, S. T. J. *Med. Chem.* **1996**, *39*, 5215.
(18) The alkyne HO-**I**-OTBDMS (10 g, 30 mmol) (see ref 19) was dissolved in ether (100 mL), and Lindlar catalyst (300 mg) was added to the solution. A balloon filled with hydrogen gas was placed on top of the reaction vessel, and the mixture was vigorously stirred at room temperature for 3 h. The catalyst was filtered off over Celite, and the solvent was removed under reduced pressure to yield the alkene HO-**H**-OTBDMS (8.3 g, 89%). ^{1}H NMR δ($CDCl_3$): 1.04 (9H, s, *tBu*); 1.7 (1H, br s, O*H*); 2.18 (2H, dt, $J = 7$ and 6 Hz, C*H*$_2$CH$_2$OH); 3.56 (2H, t, $J = 6$ Hz, CH$_2$O*H*); 4.24 (2H, d, $J = 6.5$ Hz, C*H*$_2$OSi); 5.47 (1H, m, C*H*═CH); 5.78 (1H, m, CH═C*H*); 7.41 (6H, m, *Ph*); 7.69 (4H, m, *Ph*). ^{13}C NMR δ($CDCl_3$): 19.49, 27.13, 31.35, 60.22, 62.09, 127.47, 127.85, 129.83, 132.15, 133.78, 135.76.
(19) Williams, R. M.; Kwast, A. *J. Org. Chem.* **1988**, *53*, 5785.
(20) Hayashi, N.; Fujiwara, K.; Murai, A. Tetrahedron **1997**, *53*, 12425.

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