JOC Article

A Practical Total Synthesis of Hapalosin, a 12-Membered Cyclic Depsipeptide with Multidrug Resistance-Reversing Activity, by Employing Improved Segment Coupling and Macrolactonization†

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A practical total synthesis of hapalosin, a compound with multidrug resistance-reversing activity, has been carried out using an unprecedented macrolactonization strategy. One of the features of the new approach is the straightforward and fully stereocontrolled access to the key γ-amino β-hydroxy carboxylic acid subunit via an efficient acetate aldol addition reaction with *N*-methyl α-aminoaldehydes, which relies on a camphor-derived chiral lithium acetate enolate reagent. The scope of this aldol reaction is investigated and its potential application to the synthesis of other structurally related, biologically relevant compounds illustrated. Remarkably, the chiral tether in the resulting γ-amino aldol adducts sterically protect the carbonyl group, thus avoiding intramolecular cyclization during the amino group deprotection and the subsequent segment coupling event. After successful segment coupling and smooth, clean release of the chiral auxiliary, a new macrolactonization protocol, based on the principle of double activation of both reactive sites, is applied, which leads to the 12-membered macrolactone hapalosin in unprecedented chemical efficiency.

The phenomenon of drug resistance is recognized as one of the most important obstacles in the effective treatment and cure of cancer during chemotherapy.[1] One strategy to overcome this problem is the co-administration of agents that block specific mechanisms of drug resistance. One form of drug resistance is known as multidrug resistance (MDR), and several classes of agents have been demonstrated to overcome the MDR phenotype in experimental tumor systems.[2] Despite considerable progress, the biochemical origin of MDR is not fully understood, while the molecular mechanism by which these agents are capable of overcoming MDR may be multiple.[3] Among the active anti-MDR pharmaceuticals, most share certain structural similarities from which high lipophilicity and planarity, the latter posed by the presence of two or more aromatic rings, seem to be a prerequisite for circumventing MDR.[2b] Recently, the isolation, characterization, and in vitro biological evaluation of hapalosin **1**[4] has indicated that other structural concerns may also be implicated in reversing MDR. Hapalosin is a structurally unique 12-membered cyclic depsipeptide whose molecular architecture is completely unrelated to that of the common MDR-reversing agents: it is of very low symmetry and almost free of aromatic rings. The structural backbone of **1** is comprised of the union of two hydroxy acid subunits, and one γ-amino β-hydroxy acid segment and contains five stereocenters confined in a reduced space.

The total synthesis of hapalosin was first reported by Armstrong[5] in 1995 and relied on lactone formation as the key macrocyclization step. Almost simultaneously, Ghosh[6] reported on an alternative macrocyclization through lactam formation. Later publications[7] describe several other syntheses of **1**, which also rely on this latter strategy. These works have identified two major challenging elements: the synthesis and coupling of the C6−C9 γ-amino β-hydroxy carboxylic acid subunit and the realization of the 12-membered macrocyclization. The inherent tendency of γ-amino esters to undergo intramolecular cyclization to γ-lactams is a problem posed not

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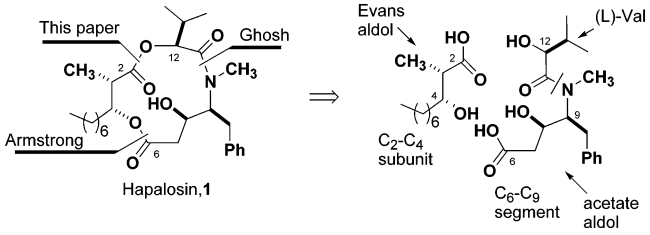


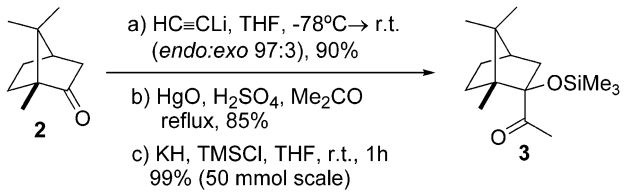
FIGURE 1. First syntheses of hapalosin along with the strategy proposed herein.

only during the synthesis and further coupling of the C6−C9 subunit, but also during the macrolactamization step, which typically proceeds in yields within the 20−40% range.[6,7] On the other hand, dimer formation usually competes with lactonization involving 10 ± 2 membered ω-hydroxy acids,[8] a problem that probably accounts for the low yield (13%) for the cyclization leading to hapalosin regardless of the reagent system employed.[5] Herein, we report a technologically advanced total synthesis of hapalosin based on an acetate aldol approach as the key reaction element to the γ-amino β-hydroxy carboxylic acid subunit along with a new macrolactonization protocol with improved chemical efficiency (Figure 1).

Results and Discussion

Acetate Aldol Reaction with *N*-Methyl α-Amino Aldehydes. The synthesis we planned begins with the construction of the C6−C9 segment followed by sequential assembly of the α-hydroxy acid unit (amide formation) and the C2−C4 propionate aldol subunit (ester formation) and final macrocyclization through the yet-unexplored lactone formation. The plan looked flexible enough to be amenable to the synthesis of analogues, and its major novelty relied on the unprecedented use of an "acetate" aldol reaction with α-amino aldehydes as the access to the γ-amino β-hydroxy carboxylic acid subunit.[9] In general, acetate aldol addition reactions tend to be poorly stereoselective,[10] while reactions involving α-amino aldehyde substrates usually require *N*,*N*-dibenzyl-protected α-amino aldehydes for success.[11] Since the nitrogen atom is methylated in the product, one optional route would begin from an otherwise protected amino group which in a latter stage would be deprotected and then methylated. A second option would begin directly from the corresponding *N*-methyl α-amino aldehyde, which would be readily available from the respective *N*-methyl α-amino acid.[12]

SCHEME 1. Preparation of Reagent 3



Prior reports from our laboratories have documented the efficiency of the lithium enolate of methyl ketone **3**, Scheme 1, in successfully addressing the problem of the insufficient stereoselectivity often encountered in the "acetate" aldol addition and related reactions.[13] On this basis, it seemed reasonable to expect that this methyl ketone reagent may be equally effective, in terms of stereoselectivity, against *N*-methyl α-amino aldehyde substrates. Furthermore, the chiral tether in reagent **3** seems to present a very crowded environment around the carbonyl group, a structural feature that may be advantageous for preventing the carbonyl function of the resulting γ-amino aldol from an eventual intramolecular cyclization event. If the above assumptions are correct, the chiral tether in **3** would act not only as the chiral controller of the process, but also as the carbonyl protecting group during segment coupling and, as a result, a straightforward access to highly functionalized γ-amino aldol subunits should be made feasible in a very concise fashion. Importantly, the synthesis of the required methyl ketone **3** from (1*R*)-(+)-camphor **2** and acetylene, two commodity chemicals available in bulk, is straightforward and high yielding, Scheme 1.

Concordant with our expectations, aldol product **5a**, from the reaction of the lithium enolate of **3** with the *N*-methyl α-amino aldehyde **4a**, Scheme 2, was indeed formed in 78% yield and, most significantly, as the sole

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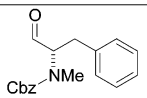
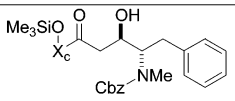
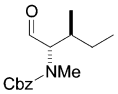
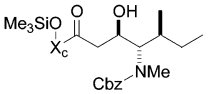
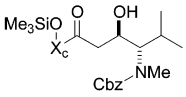
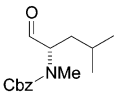
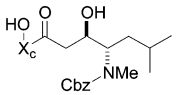
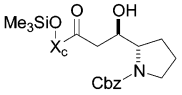
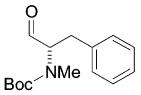
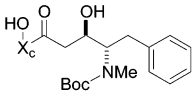
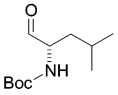
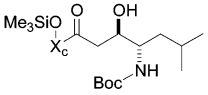
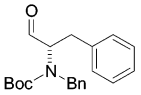
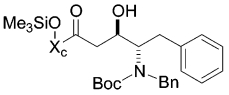
TABLE 1. Scope for the Diastereoselective Acetate Aldol Addition with α-Amino Aldehydes

Compound	Aldehyde **4**	Product[a] **5**	Yield [%][b]
a			78
b			75[c]
c			70
d			55[d]
e			65
f			70[d]
g			62
h			60

[a] For (Xc-OSiMe$_3$), see Scheme 2. [b] Yield of isolated product after silica gel chromatography. [c] Using 2 equiv of aldehyde. [d] Yield over the two steps: aldol reaction and desilylation of adducts with TBAF. For further details, see the Supporting Information.

diastereomeric product. This result appears to be quite regular for the other *N*-methyl α-amino aldehydes tested, Table 1, including *N*-BOC α-aminoaldehydes **4f**,**g**,[14] and, from the adducts obtained, diverse *γ*-amino *β*-hydroxy carboxylic acids may be formed, vide infra. Both *N*-methyl and *N*-unsubstituted *γ*-amino *β*-hydroxy carboxylic acids are found in other relevant compounds such as dolastatin,[15] didemnins,[16] and pepstatin.[17]

Concurrent with the observations noted above, it was found that methyl ketone **3** has a sterically hindered, but electronically effective, carbonyl group, and its lithium enolate may be generated simply by using *n*-BuLi as the base. Under these conditions, nucleophilic alkylation of the carbonyl group was not detected at all. This effective and unprecedented chiral tether-based carbonyl protection[18] is of particular interest in that it provides a suitable platform on which to build stereochemical motifs formally derived from the acetate aldol reaction with more complex *N*-methyl(alkyl) *N*-acyl α-amino aldehydes. For example, exposure of the aldol **5a** to hydrogen over palladium on charcoal led to the formation of the *N*-methyl derivative **6** without detection of any product derived from intramolecular attack of the amino group at the carbonyl function (Scheme 2).[19] Subsequent coupling of **6** with the acid chloride **7**, the latter prepared from the corresponding α-benzyloxy acid, provided hapalosin segment **8** in 80% yield. Deprotection of the tertiary hydroxyl group, further selective protection of the secondary carbinol as *tert*-butyldimethylsilyl(TBS) ether, and final oxidative cleavage of the acyloin moiety in the resulting **10** by using cerium ammonium nitrate (CAN),[20] afforded the required C6−C12 fragment **11** in 60% overall yield. It is also worth of noting that from this latter operation, (1*R*)-(+)-camphor, the chiral auxiliary of the approach is also released and can be easily recovered and reused. Accordingly, all carbon atomsemployed in the whole process are integrated in the final product.

Scope of the Segment-Coupling Approach. Given the results noted above, it was considered to be instructive at this stage to get some insight into the potential scope of this segment approach. For example, the synthesis of a key structural portion of the powerful antineoplastic agent dolastatin 10[15] could be made feasible in a few steps as shown in Scheme 3. Thus, *N*-methyl *γ*-amino *β*-hydroxy carbonyl adduct **5b** upon *O*-methylation[21] and subsequent exposure of the resulting *O*-methyl ether **12** to hydrogen over palladium on charcoal gave *N*-methylamine **13** as a stable intermediate whose structure was unambiguously determined by an X-ray crystal structure analysis. An amide coupling with Cbz-

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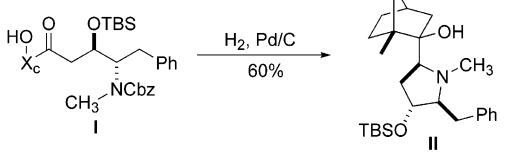
(18) For achiral appendages used to sterically protect ketone and carboxylic acid carbonyls, see the following. 1,1,1-Triphenylmethyl group: (a) Seebach, D.; Ertas, M.; Locher, R.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264−282. (b) Ertas, M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 961−968. 2,2,6,6-Tetramethylpyperidines: (c) Seebach, D.; Locher, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 957−958. 2,6-Di-*tert*-butyl-4-methoxyphenyl: (d) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087−4095. Tris-(2,6-diphenylbenzyl)silyl group: (e) Iwasaki, A.; Kondo, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 10238−10239

(19) When *N*-deprotection was carried out on substrate **I**, pyrrolidine **II** was produced as major product. An X-ray crystal-structure analysis of **II** confirmed both structure and stereochemical assignment. We thank M. C. González-Rego for the synthesis of compounds **I** and **II**.



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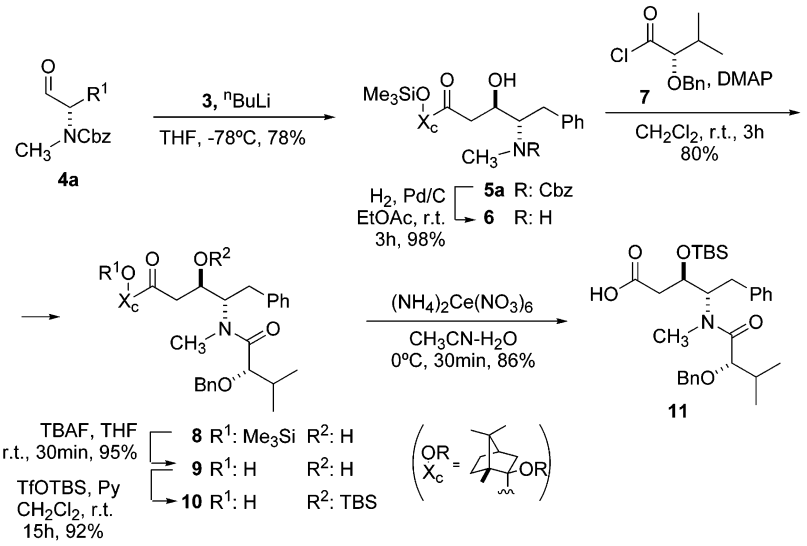
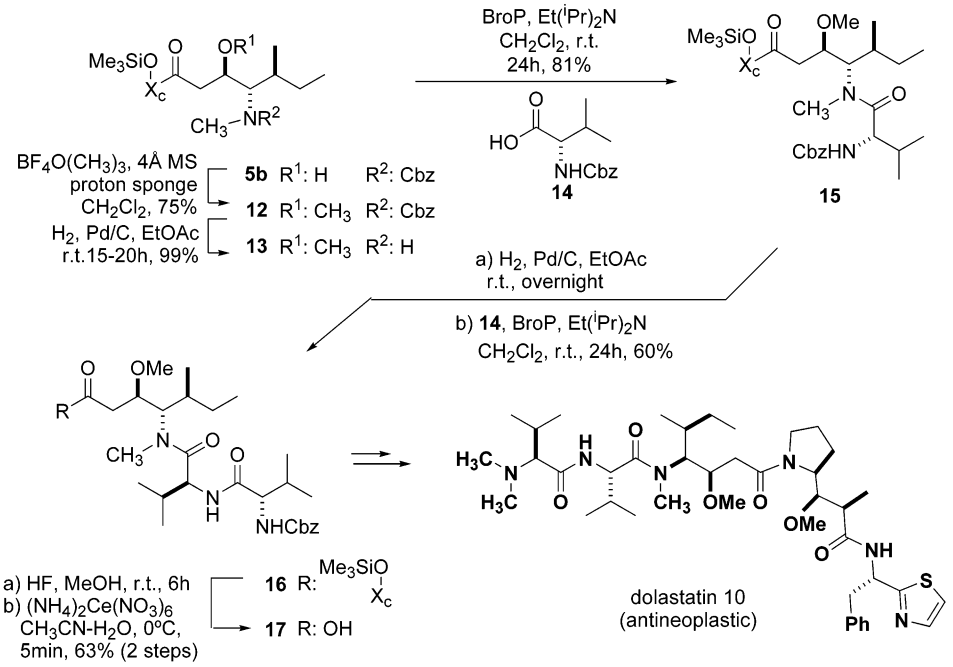
SCHEME 2. Synthesis of Segment C6−C12



SCHEME 3. Peptide Couplings en Route to Dolastatin 10



L-valine **14**, using BroP under the conditions developed by Shioiri and Hamada[22] for similar couplings, provided **15** in 81% yield. This adduct upon *N*-deprotection and further coupling with another Cbz-L-valine unit afforded coupling product **16** in 60% yield, which upon desilylation and oxidative treatment with CAN gave α,α,γ-tripeptide **17** in 63% yield over the two steps along with the recovery of camphor.

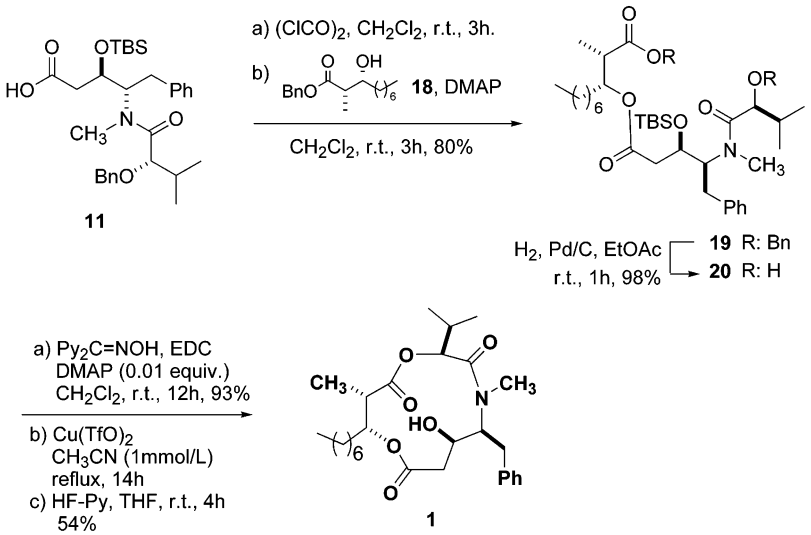
One interesting consequence of these results is that by making use of iterative couplings more complex γ-amino aldol-derived products would be accessible with minimum functional group protection/deprotection manipulations. On the other hand, from all of the above cases, it is worth noting that the scission promoted by CAN is tolerant with the methyl ether, the Cbz protecting group, and the amide function.[23]

Completion of the Synthesis of Hapalosin. Apart from the problems associated with the synthesis and coupling of the γ-amino β-hydroxy carboxylic acid segment noted above, in the reported syntheses of hapalosin the realization of the 12-membered macrocyclization also proved to be problematic. In an effort to improve earlier results, we decided to investigate the alternative yet unprecedented macrolactonization route depicted in Scheme 4. To this end, carboxylic acid **11**, upon conversion into its acid chloride and subsequent coupling with the β-hydroxy benzyl ester **18**,[7b] afforded the coupling

(22) Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913−1924.

(23) Catalytic hydrolysis of α-peptides by the action of CAN at reaction temperatures of about 50 °C has been reported recently: Takarada, T.; Yashiro, M.; Komiyama, M. *Chem. Eur. J.* **2000**, *6*, 3906−3913.

SCHEME 4. Advanced Segment Coupling and Final Macrolactonization



product **19** in 80% yield. Further deprotection of the benzyl ester and ether groups in **19** provided **20** in 98% yield, which is ready for cyclization.

The hydroxy acid **20**, however, was found to be resistant to cyclization with the use of common reagent systems such as 2,4,6-trichlorobenzoyl chloride-*N*,*N*-diisopropylethylamine (DIPEA) and DMAP,[24] 2-chloro-*N*-methylpyridinium iodide−DMAP,[25] and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)−DIPEA and DMAP.[26] In these instances, the expected cyclized product could be formed only in less than 10%−15% yields.

At this stage, we focused on methods based upon the concept of "double activation"[27] with the aid of external metal cations which in certain situations has proven to be effective for difficult macrolactonization events.[28] In particular, generation of the (*E*)-phenyl 2-pyridyl *O*-acyl oximes has been shown to be very efficient for carboxyl group activation toward *O*-alkyl and *O*-benzyl ester formation.[29] Our own group has recently documented that the related di-2-pyridyl ketone oxime esters react efficiently with α-amino acid salts to give the corresponding peptide coupling products.[30] Encouraged by these precedents, and on the basis of models depicted in Figure 2, the di-2-pyridyl ketone oxime ester of ω-hydroxy acid **20** was prepared by treatment with di-2-pyridyl ketone oxime and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) in dichloromethane in the presence of a catalytic amount of DMAP. The resulting ketone oxime ester was kinetically stable, and no spontaneous cyclization was observed in any appreciable extent. Fortunately, when 1 equiv of a metal salt, such as $Cu(OTf)_2$, was added to an acetonitrile solution of the oxime ester, a smooth reaction took place under refluxing conditions resulting in the formation of the expected cyclized product, which was desilylated by treatment with a HF−pyridine solution to afford hapalosin **1** in 54% overall yield from **20**. This is the highest yield obtained to date in this crucial macrocyclization process.[31] The ^1H NMR analysis of synthetic **1** showed the presence of cis/trans conformers around the amide function in a 2:1 ratio.

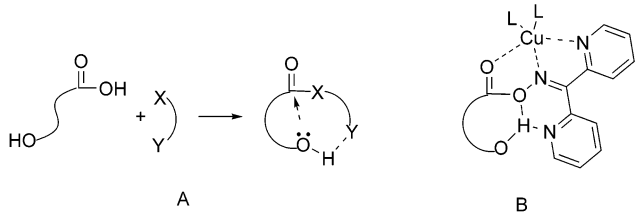


FIGURE 2. Double-activation principle[27] upon combination of di-2-pyridyl ketone oxime esters and $Cu(OTf)_2$.

Conclusions

A concise synthesis of γ-amino β-hydroxy carboxylic acid segments, which are the key structural constituents of biologically important compounds through a diastereoselective aldol methodology, is reported. The method is based on a chiral acetate reagent which shows several beneficial features: (i) aldol reactions with α-amino aldehydes occur under virtually perfect diastereocontrol; (ii) γ-amino aldol adducts show a sterically protected carbonyl group, so that no side products from intramolecular cyclization are observed; (iii) such steric protection of the carbonyl allows for subsequent coupling events to proceed in high efficiency, and again without concomitant formation of undesired side products; and (iv) the auxiliary cleavage by treatment with CAN takes place smoothly, being tolerant of the fragment functionality.

(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.
(25) (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49−52. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.
(26) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *194*, 6818−6820.
(27) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614−5616.
(28) For reviews, see: (a) Back, T. G. *Tetrahedron* **1977**, *33*, 3041−3059. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585−607. (c) Reference 8.
(29) Miyasaka, T.; Ishizu, H.; Sawada, A.; Fujimoto, A.; Noguchi, S. *Chem. Lett.* **1986**, 871−874.
(30) Palomo, C.; Palomo, A. L.; Palomo, F.; Mielgo, A. *Org. Lett.* **2002**, *4*, 4005−4008.
(31) The corresponding (*E*)-phenyl-2-pyridyl *O*-acyl oxime of acid **20** also furnished the desired cyclisized product in 40−45% yields.

Finally, it is demonstrated that the key macrocyclization to hapalosin can be carried out through a previously unrealized macrolactonization strategy, by the development of a novel macrolactonization reagent system.

Experimental Section

General Procedure for the Preparation of *N*-Methyl α-Amino Aldehydes (4). DIBAL (1 M solution in hexane, 0.04 mol, 34 mL) was added dropwise to a stirred solution of the corresponding *N*-methylamino acid methyl ester[12a] (0.02 mol) in dry toluene (60 mL) at −78 °C and under an N_2 atmosphere. The rate of addition was adjusted so as to keep the internal temperature below −65 °C. Once the addition was complete, the reaction mixture was stirred for an additional 2 h at −78 °C and then quenched by slowly adding 7.8 mL of cold (−78 °C) MeOH (H_2 evolution). The rate of addition was again adjusted so as to keep the internal temperature below −65 °C. The resulting white emulsion was slowly poured into 1 N HCl (130 mL) at 0−5 °C, and the aqueous mixture was then extracted with EtOAc (3 × 130 mL). The combined organic layers were washed with brine (130 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (mixtures of ethyl acetate/hexanes as eluent). Aldehyde **4h** was prepared in a different manner. See the Supporting Information.

General Procedure for the Aldol Reaction of the Lithium Enolate of 3 and α-Amino Aldehydes. *n*-Butyllithium (2.5M in hexane, 2.7 mL, 6.7 mmol) was added to a solution of the methyl ketone **3** (1.8 g, 6.7 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred for 1 h, and then a solution of the aldehyde **4** (4.5 mmol) in THF (9 mL) was added dropwise. After 3 h of stirring, the reaction was quenched with aqueous NH_4Cl (10 mL), the cold bath removed, and the mixture stirred until it reached room temperature. The reaction mixture was then extracted with CH_2Cl_2, and the organic layer was washed with NH_4Cl, dried over $MgSO_4$, and evaporated under vacuum**.** Purification was effected by flash column chromatography, using a 1:30 mixture of EtOAc−hexane as the eluent.

(1*R*)-2-*endo*-[(3*R*,4*S*)-4-(*N*-Benzyloxycarbonyl-*N*-methylamino)-3-hydroxy-5-phenylpentanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (5a). The procedure described above was employed at a 15 mmol aldehyde scale, with stirring at −78 °C for only 2 h instead of 3 h, to afford product **5a** as a colorless oil (6.6 g, 78%): $[\alpha]^{25}_D = -25$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3478$, 2956, 1700, 1497, 1454, 841; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.31-7.17$ (m, 10H), 4.92 (s_b, 2H), 4.17 (m, 2H), 3.18 (dd, $J = 2.9$, 14.7 Hz, 1H), 3.00 (dd, $J = 8.1$, 18.3 Hz, 1H), 2.80 (m, 1H), 2.67 (s, 3H), 2.50−2.32 (m, 2H), 1.71 (m, 1H), 1.55 (m, 1H), 1.25 (m, 1H), 1.07−0.61 (m, 3H), 1.04 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 213.5, 156.4, 138.6, 136.7, 128.2, 127.7, 127.6, 127.4, 126.0, 90.6, 69.4, 66.7, 63.2, 51.8, 50.9, 45.1, 42.9, 40.3, 33.9, 33.0, 30.1, 25.7, 20.8, 20.2, 11.1, 1.7; MS (ESI, *m*/*z*) calcd for $C_{33}H_{48}NO_5Si$ ($M + H^+$) 566.33, found 566.2.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-4-(*N*-Benzyloxycarbonyl-*N*-methylamino)-3-hydroxy-5-methylheptanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (5b). The procedure described above was employed using an aldehyde/**3** molar ratio of 2:1 (15:7.5 mmol), with stirring at −78 °C for only 30 min instead of 3 h, to afford product **5b** as a colorless oil (5.98 g, 75%): $[\alpha]^{25}_D = +8.1$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3488$, 2957, 1697, 1253, 1150, 1088, 840; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.34$ (m, 5H), 5.09 (m, 2H), 4.37 (m, 1H), 3.73 (m, 1H), 2.97 (m, 1H), 2.93 (s, 3H), 2.75 (s, 1H), 2.45 (m, 1H), 2.32 (m, 1H), 1.72 (m, 2H), 1.55 (m, 2H), 1.27 (m, 2H), 1.10−0.38 (m, 3H), 1.04 (s, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.90 (s, 3H), 0.87 (t, $J = 7.0$ Hz, 3H) 0.81 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ both rotamers = 212.9, 157.4, 136.8, 128.3, 127.8, 127.7, 127.6, 127.5, 90.6, 90.5, 68.6, 67.4, 67.1, 63.1, 51.9, 50.9, 45.2, 43.0, 40.3, 34.1, 31.7, 31.6, 30.2, 30.1, 29.1, 25.9, 25.8, 25.4, 22.7, 20.9, 20.3, 16.4, 15.7, 14.2, 11.4, 11.3, 10.9, 1.7.

(1*R*)-2-*endo*-[(3*R*)-3-((2′*S*)-*N*-Benzyloxycarbonylpyrrolidinyl)-3-hydroxypropanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (5e). The procedure described above was employed at a 15 mmol aldehyde scale, with stirring at −78 °C for only 1 h instead of 3 h, to afford product **5e** as an oil (4.89 g, 65%): $[\alpha]^{25}_D = -40$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 2956$, 1700, 1413, 841; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.37-7.28$ (m, 5H), 5.11 (d, $J = 13$ Hz, 1H), 5.04 (d, $J = 13$ Hz, 1H), 4.57 (s_b, 1H), 4.35 (m, 1H), 3.79 (m, 1H), 3.46 (m, 1H), 3.25 (m, 1H), 2.97 (dd, $J = 8.4$, 17.9 Hz, 1H), 2.47 (m, 1H), 2.29 (dd, $J = 3.3$, 17.9 Hz, 1H), 2.06−1.48 (m complex, 7 H), 1.26 (m, 1H), 1.04 (s, 3H), 0.97 (m, 1H), 0.94 (s, 3H), 0.80 (s, 3H), 0.68 (m, 1H), 0.09 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6, 90 °C) $\delta = 207.6$, 154.1, 136.8, 127.8, 127.1, 126.9, 89.9, 65.9, 65.5, 61.7, 51.0, 50.1, 46.6, 44.6, 42.6, 39.6, 29.2, 25.2, 25.0, 23.3, 20.4, 19.8, 10.5, 1.3.

(1*R*)-2-*endo*-[(3*R*,4*S*)-3-Hydroxy-4-(*N*-methylamino)-5-phenylpentanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (6). A round-bottom flask containing a mixture of **5a** (5.65 g, 10 mmol) and Pd/C (10% Pd, 1.06 g, 1 mmol) in EtOAc (100 mL) was stirred for 3 h at 25 °C under a balloon full of H_2. Then the flask was purged with N_2, and the mixture was filtered through a short column of Celite and washed well with EtOAc. The solvent was removed under reduced pressure to afford product **6** (4.23 g, 98%): $[\alpha]^{25}_D = +20$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3467$, 2956, 1707, 1454, 1122, 841; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.32-7.16$ (m, 5H), 4.16 (m, 1H), 3.06 (dd, $J = 9.2$, 17.9 Hz, 1H), 2.82−2.36 (m, 4H), 2.38 (s, 3H), 1.83−0.64 (m, 7H), 1.03 (s, 3H), 1.01 (s, 3H), 0.80 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 211.5$, 138.7, 129.0, 128.4, 126.2, 90.6, 66.2, 64.5, 51.7, 50.8, 45.1, 41.1, 40.1, 35.0, 34.5, 30.0, 25.7, 20.9, 20.3, 11.3, 1.7; MS (ESI, *m*/*z*) calcd for $C_{25}H_{42}NO_3Si$ ($M + H^+$) 432.30, found 432.5.

(2*S*)-Benzyloxy-3-methylbutanoyl Chloride (7). A solution of $LiOH\cdot H_2O$ (1.68 g, 40 mmol) in water (6.8 mL) was added dropwise to a solution of methyl (2*S*)-benzyloxy-3-methylbutanoate[32] (2.22 g, 10 mmol) in methanol (20 mL) at room temperature. The mixture was stirred at reflux for 3 h, and then water (15 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the aqueous layer was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give (2*S*)-benzyloxy-3-methylbutanoic acid: yield 1.89 g, 91%; $[\alpha]^{25}_D = -84.0$ ($c = 1.0$, THF); IR (neat) $\nu = 3180$, 2965, 1712, 1454, 1208, 1071, 697; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.34-7.29$ (m, 5H), 4.71 (d, $J = 11.9$ Hz, 1H), 4.46 (d, $J = 11.6$ Hz, 1H), 3.79 (d, $J = 4.6$ Hz, 1H), 2.15 (m, 1H), 1.01 (d, $J = 2.9$ Hz, 3H), 0.98 (d, $J = 2.9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 177.8$, 137.1, 128.3, 127.9, 127.8, 82.6, 72.8, 31.5, 18.9, 17.4. To a solution of this acid (1.25 g, 6 mmol) in CH_2Cl_2 (24 mL) cooled to 0 °C was added dropwise oxalyl chloride (1.55 mL, 18 mmol). The mixture was stirred at room temperature for 3 h, the solvent and excess oxalyl chloride were removed under reduced pressure, and the crude product was used in the next reaction as is.

(1*R*)-2-*endo*-[(3*R*,4*S*)-4-(*N*-((*S*)-2-Benzyloxy-3-methylbutanoyl)-*N*-methylamino)-3-hydroxy-5-phenylpentanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (8). To a solution of **6** (2.16 g, 5 mmol) and DMAP (1.47 g, 12 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C was added a solution of (2*S*)-benzyloxy-3-methylbutanoyl chloride **7** (1.36 g, 6 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 3 h and then washed with 1 N HCl (3 × 20 mL) and with a saturated solution of $NaHCO_3$ (2 × 20 mL).

(32) Sly, W.-R.; Swing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659−7672.

The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc−hexane 1:40) to afford product **8** as a solid (2.49 g, 80%): mp 115−116 °C; $[\alpha]^{25}_D = -57.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3443, 2958, 1702, 1635, 1497, 1454, 1150, 842$; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta =$ 7.30−7.09 (m, 10H), 4.87 (m, 1H), 4.80 (m, 1H), 4.25 (m, 1H), 3.91 (d, $J = 11.0$ Hz, 1H), 3.78 (d, $J = 6.2$ Hz, 1H), 3.72 (d, $J = 12.8$ Hz, 1H), 3.10 (dd, $J = 8.8, 17.6$ Hz, 1H), 3.10 (m, 1H), 2.88 (m, 1H), 2.88 (s, 3H), 2.48 (d, $J = 4.4$ Hz, 1H), 2.21 (d, $J = 17.6$ Hz, 1H), 1.76 (m, 3H), 1.56 (m, 1H), 1.26 (m, 1H), 1.08−0.71 (m, 2H), 1.05 (s, 3H), 0.92 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.80 (s, 3H), 0.78 (d, $J = 6.6$ Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 213.0, 172.3, 138.3, 137.8, 129.3, 129.0, 128.6, 128.4, 128.1, 127.7, 127.5,127.4, 126.4, 90.7, 83.0$ (broad), 70.7, 70.0, 51.9, 51.0, 45.2, 43.2, 40.4, 32.0, 30.6, 30.3, 25.8, 20.9, 20.3, 19.3, 18.4, 11.5, 1.8; MS (ESI, *m*/*z*) calcd for $C_{37}H_{56}NO_5Si$ ($M + H^+$) 622.39, found 622.4. Anal. Calcd for $C_{37}H_{55}NO_5Si$ (621.93): C, 71.44; H, 8.93; N, 2.25. Found: C, 71.48; H, 8.91; N, 2.27.

(1*R*)-2-*endo*-[(3*R*,4*S*)-4-(*N*-((2*S*)-Benzyloxy-3-methylbutanoyl)-*N*-methylamino)-3-hydroxy-5-phenylpentanoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (9). To a solution of **8** (1.86 g, 3 mmol) in THF (60 mL) was added TBAF (1 M in THF, 4.5 mL, 4.5 mmol) at room temperature, and the mixture was stirred for 30 min at the same temperature. Then, the solvent was removed under reduced pressure and the crude was filtered through a short column of silica gel using CH_2Cl_2 as eluant. The solvent was removed under reduced pressure to afford compound **9** as a solid (1.57 g, 95%): mp 130−131 °C; $[\alpha]^{25}_D = -77.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3381, 2957, 1702, 1631, 1496, 1454, 1082$; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.30-7.09$ (m, 10H), 4.93 (s, 1H), 4.83 (m, 1H), 4.83 (d, $J = 5.5$ Hz, 1H), 4.15 (m, 1H), 3.97 (d, $J = 11.7$ Hz, 1H), 3.77 (d, $J = 11.0$ Hz, 1H), 3.75 (d, $J = 4.0$ Hz, 1H), 3.21 (m, 1H), 3.17 (dd, $J = 8.8, 16.1$ Hz, 1H), 2.88 (m, 1H), 2.88 (s, 3H), 2.26 (m, 2H), 1.85 (m, 1H), 1.78−1.51 (m, 3H), 1.26 (m, 1H), 1.12−0.73 (m, 2H), 1.12 (s, 3H), 0.94 (s, 3H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.80 (s, 3H), 0.75 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 214.1, 173.6, 138.0, 137.5, 130.8, 129.2, 128.8, 128.4, 128.1, 127.7, 127.5, 127.2, 126.8, 126.5, 87.8, 84.2, 71.1, 51.7, 51.0, 45.1, 41.4, 32.8, 30.6, 30.3, 26.2, 20.9, 20.6, 18.9, 18.7, 11.3, 1.0; MS (ESI, *m*/*z*) calcd for $C_{34}H_{48}NO_5$ ($M + H^+$), 550.36, found 550.4. Anal. Calcd for $C_{34}H_{47}NO_5$ (549.75): C, 74.27; H, 8.63; N, 2.55. Found: C, 74.32; H, 8.61; N, 2.57.

(1*R*)-2-*endo*-[(3*R*,4*S*)-4-(*N*-((*S*)-2-Benzyloxy-3-methylbutanoyl)-*N*-methylamino)-3-*tert*-butyldimethylsilyloxy-5-phenylpentanoyl]-1,7,7-trimethylbicyclo[2.2.1]hep-tan-2-ol (10). Pyridine (1.44 mL, 17.8 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.75 mL, 12 mmol) were added to a solution of **9** (1.65 g, 3 mmol) in CH_2Cl_2 (15 mL) at room temperature. The mixture was stirred at this temperature for 15 h and then was washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). Purification was effected by flash column chromatography (EtOAc−hexane 1:10) to give compound **10** as a colorless oil (1.83 g, 92%): $[\alpha]^{25}_D = -39.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3381, 2956, 2931, 1697, 1626, 1454, 1083$; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.30-7.12$ (m, 10H), 4.92 (m, 1H), 4.72 (s, 1H), 4.45 (m, 1H), 3.93 (d, $J = 12.1$ Hz, 1H), 3.77 (d, $J = 6.2$ Hz, 1H), 3.73 (d, $J = 12.1$ Hz, 1H), 3.27 (dd, $J = 5.9, 17.9$ Hz, 1H), 3.15 (dd, $J = 15.4, 4.0$ Hz, 1H), 2.90 (m, 1H), 2.90 (s, 3H), 2.42 (dd, $J = 3.7, 17.6$ Hz, 1H), 2.25 (d, $J = 12.5$ Hz, 1H), 1.89−1.48 (m, 4H), 1.25 (m, 1H), 1.14−0.74 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.92 (s, 9H), 0.86 (d, $J = 5.5$ Hz, 3H), 0.80 (s, 3H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.14 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 211.1, 172.6, 138.1, 137.5, 128.7, 128.4, 128.2, 127.9, 127.7, 127.3, 126.3, 87.7, 81.4, 72.0, 70.4, 58.0, 51.8, 51.0, 48.4, 45.1, 41.9, 31.4, 30.6, 30.3, 26.2, 26.0, 25.9, 25.7, 21.0, 20.7, 18.7, 18.4, 17.9, 11.1, −3.7, −4.7; MS (ESI, *m*/*z*) calcd for $C_{40}H_{62}NO_5Si$ ($M + H^+$) 664.44, found 664.5.

(3*R*,4*S*)-4-(*N*-((*S*)-2-Benzyloxy-3-methylbutanoyl)-*N*-methylamino)-3-*tert*-butyldimethylsilyloxy-5-phenylpentanoic Acid (11). A solution of cerium ammonium nitrate (CAN) (3.28 g, 6 mmol) in water (12 mL) was added dropwise to a solution of **10** (1.33 g, 2 mmol) in acetonitrile (24 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. Then water (6 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:10) to afford (1*R*)-(+)-camphor in the first fractions and compound **11** in the subsequent fractions (0.91 g, 86%): mp 118 °C; $[\alpha]^{25}_D = -60.5$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu =$ 2957, 2930, 1729, 1620, 1497, 1470, 836; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 11.00$ (s_b, 1H), 7.30−7.05 (m, 10H), 4.40 (m, 1H), 4.20 (d, $J = 12.1$ Hz, 1H), 3.63 (d, $J = 6.6$ Hz, 1H), 3.63 (m, 1H), 3.27 (d, $J = 6.6$ Hz, 1H), 2.84 (s, 3H), 2.84−2.38 (m, 4H), 1.84 (m, 1H), 0.96 (s, 9H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.70 (d, $J = 6.6$ Hz, 3H), 0.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 174.7, 172.8, 138.0, 137.6, 128.8, 128.6, 128.3, 128.1, 127.9, 127.7, 127.6, 127.3, 126.4, 82.1, 70.7, 70.2, 40.9, 33.9, 30.2, 25.8, 19.1, 17.9, −4.1, −4.7; MS (ESI, *m*/*z*) calcd for $C_{30}H_{44}NO_5Si$ ($M - H^+$) 526.30, found 526.4. Anal. Calcd for $C_{30}H_{45}NO_5Si$ (527.85): C, 68.26; H, 8.61; N, 2.65. Found: C, 68.32; H, 8.59; N, 2.67.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-4-(*N*-Benzyloxycarbonyl-*N*-methylamino)-3-methoxy-5-methylheptanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (12). Proton Sponge (1.393 g, 6.5 mmol) and trimethyloxonium tetrafluoroborate (0.924 g, 6.25 mmol) were added to a solution of **5b** (1.33 g, 2.5 mmol) in CH_2Cl_2 (30 mL) over 4 Å molecular sieves 4 Å (1.1 g) at 0 °C. The mixture was stirred at room temperature for 24 h and then was filtered through a short column of Celite, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:35): yield 1.02 g, 75%; $[\alpha]^{25}_D = +7.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 2958, 1701, 1251, 1151, 1089, 841$; ^{1}H NMR (200 MHz, $CDCl_3$) (data of both rotamers unless otherwise noted) $\delta = 7.31$ (s_b, 5H), 5.16 (d, $J = 13.2$ Hz, 1H), 5.07 (d, $J = 13.2$ Hz, 1H), 4.03 (m, 2H), 3.33 (s, 3H, single rotamer), 3.22 (s, 3H, single rotamer), 3.20 (m, 1H), 2.78 (s, 3H), 2.54 (dd, $J = 5.1, 11.7$ Hz, 1H), 2.17 (d_b, $J = 18.3$ Hz, 1H), 1.80−0.45 (m, 9H, complex), 1.02 (s, 3H), 0.88 (m, 9H), 0.79 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (both rotamers) = 208.5, 208.4, 157.1, 157.0, 137.1, 136.8, 128.2, 127.9, 127.7, 127.5, 127.3, 90.4, 76.1, 76.0, 67.2, 66.7, 60.1, 57.9, 57.8, 51.4, 50.8, 45.2, 40.8, 40.2, 33.7, 33.4, 31.5, 30.9, 29.9, 26.0, 25.9, 25.8, 20.9, 20.3, 16.1, 16.0, 11.3, 10.8, 2.2, 1.6, 1.0.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-3-Methoxy-5-methyl-4-(*N*-methylamino)heptanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (13). A round-bottom flask containing a mixture of **12** (0.457 g, 0.835 mmol) and Pd/C (10% Pd, 0.089 g, 0.08 mmol) in EtOAc (4 mL) was stirred overnight at 25 °C under a balloon full of H_2. Then the flask was purged with N_2, and the mixture was filtered through a short column of Celite and washed well with EtOAc. The solvent was removed under reduced pressure to afford product **13** (0.342 g, 99%): mp 70−71 °C; $[\alpha]^{25}_D = +5.9$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 2958, 2933, 2876, 1252, 1088, 841$; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.91$ (m, 1H), 3.29 (s, 3H), 3.19 (dd, $J = 9.5, 19.0$ Hz, 1H), 2.53 (d, $J = 11.7$ Hz, 1H), 2.46 (m, 1H), 2.44 (s, 3H), 2.22 (dd, $J = 2.3, 12.0$ Hz, 1H), 1.76−0.64 (m, 6H, complex), 1.00 (s, 3H), 0.95 (s, 3H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.84 (d, $J = 7.3$ Hz, 3H), 0.77 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 208.6, 90.5, 76.3, 65.0, 57.5, 51.7, 50.8, 45.2, 40.3, 39.9, 35.9, 29.8, 26.0, 25.8, 20.9, 20.3, 16.0, 11.9, 11.3, 1.8, 1.7, 1.0.$ Anal. Calcd for $C_{23}H_{45}NO_3Si$ (411.69): C, 67.10; H, 11.02; N, 3.40. Found: C, 66.98; H, 11.15; N, 3.62.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-4-(*N*-((2*S*)-*N*-Benzyloxycarbonylamino-3-methylbutanoyl)-*N*-methylamino)-3-methoxy-

5-methylheptanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (15). Diisopropylethylamine (0.118 mL, 0.68 mmol) was added to a solution of *N*-Cbz-L-valine **14** (0.1005 g, 0.4 mmol), **13** (0.0825 g, 0.2 mmol), and bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP)[22] (0.1164 g, 0.3 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was shielded from light and stirred at 0 °C for 10 min and then at room temperature for 24 h. The mixture was washed with 1 M aqueous $KHSO_4$ (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (25 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:35): yield 0.104 g, 81%; $[\alpha]^{25}_D = +2.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu =$ 2958, 1712, 1637, 1251, 842; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.34$ (s_b, 5H), 6.79 (d, $J = 8.8$ Hz, 1H), 5.10 (d, $J =$ 12.4 Hz, 1H), 5.01 (d, $J = 12.4$ Hz, 1H), 4.60 (m, 1H), 4.32 (dd, $J = 7.3$, 8.8 Hz, 1H) 4.04 (m, 1H), 3.27 (s, 3H), 3.11 (dd, $J = 9.5$, 18.3 Hz, 1H), 2.97 (s, 3H), 2.50 (m, 1H), 2.29 (dd, $J =$ 1.5, 18.3 Hz, 1H), 2.10 (m, 1H), 1.79 (m, 3H), 1.59 (m, 1H), 1.29 (m, 2H), 1.06−0.75 (m, 3H, complex), 1.02 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.80 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ both rotamers = 208.0, 173.8, 156.9, 138.0, 129.0, 128.4, 128.1, 90.6, 76.6, 65.9, 58.2, 57.2, 51.9, 51.2, 45.4, 32.4, 30.5, 30.2, 26.3, 26.1, 21.6, 20.9, 19.8, 19.1, 16.4, 11.8, 10.9, 2.4, 2.2.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-4-(*N*-((2*S*)-((2*S*)-*N*-benzyloxycarbonylamino-3-methylbutanoyl)-3-methylbutanoyl)-*N*-methylamino)-3-methoxy-5-methylheptanoyl]-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (16). A round-bottom flask containing a mixture of **15** (0.0594 g, 0.092 mmol) and Pd/C (10% Pd, 0.0098 g, 0.0092 mmol) in EtOAc (0.5 mL) was stirred overnight at 25 °C under a balloon full of H_2. Then the flask was purged with N_2, and the mixture was filtered through a short column of Celite and washed well with EtOAc. The solvent was removed under reduced pressure to afford a product (0.0465 g, 99%) which was used in the next reaction without further purification.

Diisopropylethylamine (0.945 mL, 5.44 mmol) was added to a solution of *N*-Cbz-L-valine **14** (0.8041 g, 3.2 mmol), the above product (0.8142 g, 1.6 mmol), and bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP) (0.9313 g, 2.4 mmol) in CH_2Cl_2 (18 mL), and the resulting mixture was shielded from light and stirred at 0 °C for 10 min and then at room temperature for 24 h. The mixture was washed with 1 M aqueous $KHSO_4$ (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (25 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:5): yield 0.7143 g, 60%; mp 178−179 °C; $[\alpha]^{25}_D = -15.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3283$, 2959, 2873, 1712, 1631, 1245; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta = 7.63$ (d, $J = 8.8$ Hz, 1H), 7.36 (m, 5H), 6.83 (d, $J = 8.8$ Hz, 1H), 5.05 (s, 2H), 4.63 (m, 2H), 4.01 (m, 2H), 3.27 (s, 3H), 3.12 (dd, $J = 9.5$, 18.3 Hz, 1H), 2.97 (s, 3H), 2.50 (m, 1H), 2.10 (m, 2H), 1.80 (m, 2H), 1.60 (m, 1H), 1.27 (m, 2H), 1.07−0.78 (m, 4H, complex), 0.09 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ both rotamers = 207.5, 172.8, 170.9, 156.1, 136.3, 128.3, 127.9, 90.3, 75.5, 66.8, 60.2, 57.8, 55.9, 55.8, 54.3, 54.4, 50.8, 45.2, 40.1, 39.6, 32.7, 31.5, 31.2, 30.1, 25.8, 20.9, 20.3, 19.4, 19.1, 17.8, 17.6, 15.5, 11.4, 10.4, 1.5. Anal. Calcd for $C_{41}H_{69}N_3O_7Si$ (744.09): C, 66.18; H, 9.35; N, 5.65. Found: C, 65.86; H, 9.48; N, 5.76.

(1*R*)-2-*endo*-[(3*R*,4*S*,5*S*)-4-(*N*-((2*S*)-((2*S*)-*N*-Benzyloxycarbonylamino-3-methylbutanoyl)-3-methylbutanoyl)-*N*-methylamino)-3-methoxy-5-methylheptanoic Acid (17). HF (48% aqueous solution) (1.5 mL) was added to a solution of **16** (0.5778 g, 0.78 mmol) in methanol (6 mL) at room temperature, and the mixture was stirred for 6 h at the same temperature. Then, the mixture was neutralized with a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure. The crude product was used in the next reaction without further purification. A solution of cerium ammonium nitrate (CAN) (1.28 g, 2.3 mmol) in water (5 mL) was added dropwise to a solution of the above crude in acetonitrile (9 mL) at 0 °C, and the mixture was stirred at the same temperature for 5 min. Then water (6 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant: ethyl acetate/hexane 1:10) to afford (1*R*)-(+)-camphor in the first fractions and compound **17** in the subsequent fractions (0.263 g, 63%): mp 134−135 °C; $[\alpha]^{25}_D = -36.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3400$, 2969, 2933, 1702, 1630, 1379; ^{1}H NMR (200 MHz, DMSO-d_6, 90 °C) $\delta =$ 7.62 (d, $J = 8.8$ Hz, 1H), 7.34 (s_b, 5H), 6.83 (d, $J = 8.8$ Hz, 1H), 5.91 (s_b, 1H), 5.04 (s, 2H), 4.60 (m, 1H), 4.48 (m, 1H), 3.94 (m, 2H), 3.27 (s, 3H), 2.93 (s, 3H), 2.60−1.62 (m, 5H, complex), 1.30 (m, 2H), 0.80 (m, 18H, complex); ^{13}C NMR (50 MHz, $CDCl_3$) δ both rotamers = 173.1, 171.6, 156.6, 137.8, 137.7, 129.6, 128.9, 128.4, 128.3, 127.7, 126.0, 79.2, 66.1, 60.3, 57.7, 54.8, 33.3, 32.3, 31.3, 31.0, 26.2, 21.9, 20.0, 19.8, 19.3, 18.9, 16.6, 11.4. Anal. Calcd for $C_{28}H_{45}N_3O_7$ (535.67): C, 62.78; H, 8.47; N, 7.84. Found: C, 63.02; H, 8.72; N, 6.59.

Benzyl (2*S*,3*R*)-3-((3*R*,4*S*)-4-*N*-((*S*)-2-Benzyloxy-3-methylbutanoyl)-*N*-methylamino-3-*tert*-butyldimethylsilyloxy-5-phenylpentanoyloxy)-2-methyldecanoate (19). Oxalyl chloride (0.30 mL, 4.5 mmol) was added dropwise to a solution of **11** (0.79 g, 1.5 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C. The mixture was stirred at room temperature for 3 h, and then the solvent and excess oxalyl chloride were removed under reduced pressure and the crude product was used in the next reaction as is. A solution of the acid chloride (1.5 mmol) in CH_2Cl_2 (1.5 mL) was added to a cooled (0 °C) solution of benzyl (2*S*,3*R*)-3-hydroxy-2-methyldecanoate **18**[7b] (0.44 g, 1.5 mmol) and DMAP (0.46 g, 3.75 mmol) in CH_2Cl_2 (7.5 mL). The resulting solution was stirred at room temperature for 3 h, and then it was washed with 1 N HCl (3 × 10 mL) and with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane 1:50) to afford compound **19** as an oil (0.96 g, 80%): $[\alpha]^{25}_D = -37.0$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 2956$, 2928, 1735, 1653, 1497, 1456, 836; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.34-7.00$ (m, 15H), 5.11 (m, 1H), 5.03 (s, 2H), 4.40 (m, 1H), 4.13 (d, $J = 11.4$ Hz, 1H), 3.57 (d, $J = 7.0$ Hz, 1H), 3.57 (m, 1H), 3.27 (dd, $J = 7.0$, 14.7 Hz, 1H), 2.75 (s, 3H), 2.75−2.49 (m, 5H), 1.82 (m, 1H), 1.49 (m, 2H), 1.20 (m, 10H), 1.08 (d, $J = 7.3$ Hz, 3H), 0.87 (m, 6H), 0.87 (s, 9H), 0.67 (d, $J = 7.0$ Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 173.4, 171.9, 171.0, 138.4, 138.0, 135.8, 129.0, 128.7, 128.5, 128.4, 128.2, 128.0, 127.7, 127.6, 127.3, 126.4, 82.5, 74.7, 70.5, 70.0, 66.4, 43.0, 40.3, 34.2, 32.0, 31.8, 30.3, 29.4, 29.2, 26.0, 25.5, 22.7, 19.2, 18.1, 14.1, 12.3, −3.9, −4.6; MS (ESI, *m*/*z*) calcd for $C_{48}H_{72}NO_7Si$ ($M + H^+$) 802.51, found 802.5.

(2*S*,3*R*)-3-((3*R*,4*S*)-3-*tert*-Butyldimethylsilyloxy-4-*N*-((*S*)-2-hydroxy-3-methylbutanoyl)-*N*-methylamino-5-phenylpentanoyloxy)-2-methyldecanoic Acid (20). A round-bottom flask containing a mixture of **19** (0.80 g, 1 mmol) and Pd/C (10% Pd, 0.106 g, 0.1 mmol) in EtOAc (2 mL) was stirred for 1 h at 25 °C under a balloon full of H_2. Then the flask was purged with N_2 and the mixture was filtered through a short column of Celite and washed well with EtOAc. The solvent was removed under reduced pressure to afford product **20** as an oil (0.61 g, 98%): $[\alpha]^{25}_D = -20.5$ ($c = 1.0$, CH_2Cl_2); IR (neat) $\nu = 3432$, 2956, 2929, 1737, 1640, 1464, 1083, 837; ^{1}H NMR (500 MHz, $CDCl_3$) (data of both rotamers unless otherwise noted) $\delta = 7.25-7.10$ (m, 5H), 5.33 (m, 1H), 4.35 (m, 1H,

corresponding to single rotamer), 3.97 (m, 1H, single), 3.41 (d, $J = 7.3$ Hz, 1H, single), 3.32 (dd, $J = 14.1$, 2.4 Hz, 1H, single), 3.23 (dd, $J = 13.8$, 3.4 Hz, 1H, single), 3.10 (dd, $J = 8.2$, 18.7 Hz, 1H, single), 2.89 (s, 3H, single), 2.77−2.60 (m, 1H both, 4H single), 2.54−2.43 (m, 1H both, 1H single), 1.63 (m, 1H both, 1H single), 1.50 (m, 1H both, 2H single), 1.28 (m, 12H both, 1H single), 1.16 (d, $J = 6.8$ Hz, 3H, single), 1.10 (d, $J = 6.8$ Hz, 3H, single), 0.98−0.83 (m, 4H both, 6H single), 0.96 (s, 9H, single), 0.94 (s, 9H, single), 0.65 (d, $J = 6.8$ Hz, 3H, single), 0.18 (d, $J = 6.8$ Hz, 3H, single), 0.17 (s, 3H, single), 0.14 (s, 3H, single), 0.12 (s, 3H, single), 0.08 (s, 3H, single); ^{13}C NMR (50 MHz, $CDCl_3$) δ of major rotamer = 177.7, 174.4, 170.5, 137.8, 129.0, 128.7, 128.3, 126.3, 74.4, 72.6, 69.5, 64.6, 42.7, 40.3, 34.2, 31.7, 30.4, 29.1, 25.9, 25.8, 22.6, 20.0, 18.0, 15.0, 14.1, 11.5, −4.0, −4.8; MS (ESI, *m*/*z*) calcd for $C_{34}H_{59}NO_7Si$ ($M - H^+$) 620.40, found 620.3.

Hapalosin (1). EDC (0.26 g, 1.4 mmol), di-2-pyridyl ketone oxime (0.19 g, 1 mmol), and DMAP (1 mg, 0.01 mmol) were added successively to a solution of the crude acid **20** (0.62 g, 1 mmol) in CH_2Cl_2 (0.5 mL) at room temperature, and the mixture was stirred for 12 h at the same temperature. Then, CH_2Cl_2 (15 mL) was added, and the mixture was washed with 1 M $KHSO_4$ (10 mL) and with water (2 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure. The crude product was used in the next reaction without further purification. Yield crude: 0.74 g, 93%. A solution of the dipyridyl *O*-acyl oxime (0.36 g, 0.47 mmol) and $Cu(TfO)_2$ (0.18 g, 0.50 mmol) in acetonitrile (460 mL) was stirred at reflux for 14 h. The solvent was then removed under reduced pressure, and after addition of CH_2Cl_2 (15 mL), the mixture was washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure. The crude was dissolved in THF (10 mL), and then HF/pyridine complex (Aldrich) (2 mL) was added dropwise at room temperature and the mixture was stirred for 4 h. Then a saturated solution of $NaHCO_3$ was added to remove excess acid, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (ethyl acetate/hexane 1:15) to afford hapalosin **1** as a colorless oil that solidified on standing (0.124 g, 54%). Data of the mixture of two conformers: $[\alpha]^{25}_D = -40$ ($c = 1.0$, CH_2Cl_2); IR (neat) ν = 3411, 2959, 1731, 1631, 1496, 1456, 1151; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.34$ (dd, $J = 7.0$, 7.7 Hz, 2H), 7.26−7.19 (m, 3H), 5.13 (m, 1H), 4.32 (d, $J = 8.4$ Hz, 1H), 3.86 (m, 1H), 3.70 (dt, $J = 8.8$, 2.5 Hz, 1H), 3.41 (dd, $J = 13.9$, 2.5, 1H), 3.24 (m, 1H), 2.93 (dd, $J = 5.3$, 17.9 Hz, 1H), 2.86 (s, 3H), 2.65 (m, 1H), 2.62 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.62 (m, 1H), 1.40−1.20 (m_b, 10H), 1.18 (d, $J = 6.9$ Hz, 3H), 0.89 (m, 3H), 0.56 (d, $J = 6.9$ Hz, 3H), 0.24 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.6, 171.7, 170.4, 170.0, 168.6, 168.5, 137.7, 137.3, 129.1, 128.9, 128.7, 128.2, 126.9, 126.2, 82.9, 76.5, 74.8, 73.8, 70.1, 61.3, 59.0, 40.9, 40.7, 40.3, 37.3,36.2, 35.3, 31.7, 31.7, 30.6, 29.4, 29.2, 29.1, 28.9, 28.1, 26.0, 25.2, 22.6, 19.6, 18.3, 17.6, 16.6, 14.1, 12.1, 10.4; MS (ESI, *m*/*z*) calcd for $C_{28}H_{44}NO_6$ ($M + H^+$) 490.32, found 490.3.

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Supporting Information Available: Experimental procedures, characterization data for compounds **5c**,**d**,**f**−**h**, ^{1}H and ^{13}C NMR spectra of compounds **1**, **5a**, **6**, **8**−**13**, **15**−**17**, **19**, **20**, and X-ray crystallographic data for compounds **13** and **II** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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