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# Stereoselective Synthesis of C-Substituted Morpholine Derivatives using Reductive Etherification Reaction: Total Synthesis of Chelonin C

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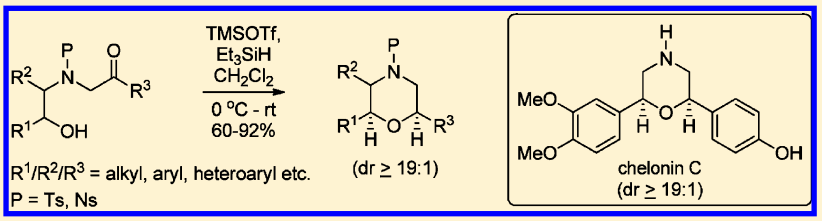
Supporting Information




**ABSTRACT:** A general strategy is developed for the stereoselective synthesis of C-substituted morpholine derivatives using intramolecular reductive etherification reaction. The method is extended to the first stereoselective total synthesis of (±)-chelonin C.

Recently, morpholines or 1,4-oxazine derivatives have attracted considerable attention owing to the biological activity associated with this motif.[1] Morpholine derivatives have also found application in the enantioselective synthesis as chiral organocatalysts,[2] chiral auxiliaries,[3] and chiral templates in the synthesis of α-hydroxy acids and oxacycles.[4] Among morpholines, 2,5- and 2,6-disubstituted morpholines are particularly important as they are found in many biologically important natural products (Figure 1).

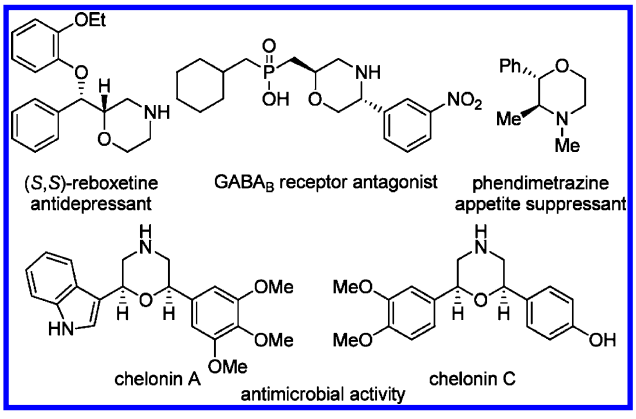


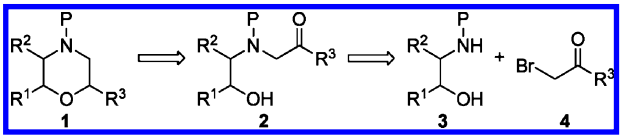

**Figure 1.** Bioactive compounds bearing a morpholine moiety.

Not surprisingly, some progress has been made on the synthesis of 2,5- and 2,6-disubstituted morpholine derivatives.[5] However, there are still some challenges; e.g., typically 2,5- and 2,6-disubstituted morpholine derivatives are prepared by a two-component disconnection involving C−O ether bond formation, typically by Williamson's etherification reaction. Here, both the fragments required have to be prepared in enantiomerically enriched forms or a mixture of stereoisomers is obtained. Further, very few reports described in the literature provide a general, highly stereoselective access to differently substituted morpholines.[6]

In continuation of our program directed at developing stereoselective synthesis of oxa- and azacycles,[7] herein, we report a concise strategy which is applicable to the stereoselective synthesis of a broad range of C-substituted morpholine derivatives using reductive etherification as a key reaction.

We envisioned a general approach for the synthesis of morpholines **1** by disconnecting the C−O bond similar to many other approaches but relying on reductive etherification reaction[8] rather than the Williamson's etherification reaction. It was argued that the oxocarbenium ion intermediate derived from keto alcohol **2** using an appropriate Lewis acid could be reduced in a highly stereoselective fashion using triethylsilane to generate morpholines. The keto alcohol **2** in turn could be rapidly assembled from readily available N-protected 1,2-amino alcohols **3** and α-bromo ketones **4** (Scheme 1).

**Scheme 1. Retrosynthesis for the Synthesis of Morpholine Derivatives**




In order to test the strategy, the *N*-tosylethanolamine (**3a**) was reacted with bromoacetone (**4a**) to furnish the keto alcohol

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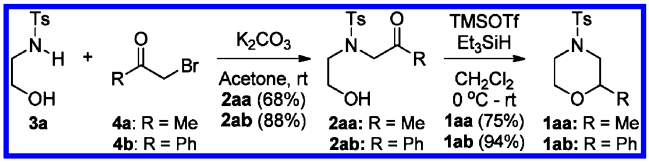
**2aa**.[9] Treatment of keto alcohol **2aa** with TMSOTf and $Et_3SiH$ for 1 h gratifyingly furnished the morpholine derivative **1aa**[5g] in good yield (Scheme 2). Similarly, reaction of the keto alcohol

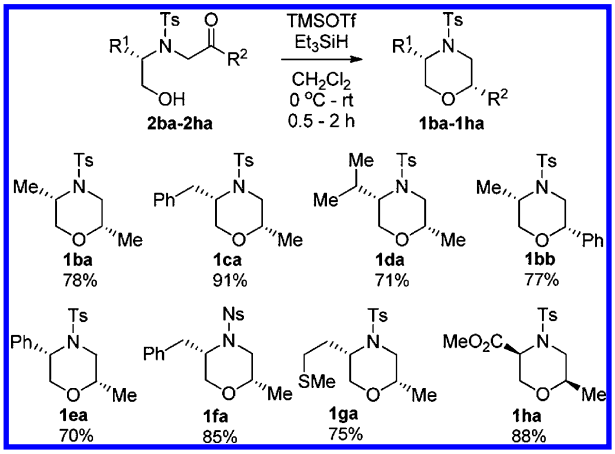
**Scheme 2. Synthesis of Monosubstituted Morpholine Derivatives**




**2ab** derived from *N*-tosylethanolamine (**3a**) and phenacyl bromide (**4b**) gave the morpholine **1ab**[5h] in excellent yield.

Encouraged by these results, we embarked on the synthesis of 2,5-disubstituted morpholines. Toward this end, the keto alcohols **2ba–ha** were prepared by N-alkylation of enantiomerically enriched amino alcohols **3b–h** with $\alpha$-bromo ketones **4a–b**. Scheme 3 outlines the scope of this reductive etherification

**Scheme 3. Stereoselective Synthesis of *cis*-2,5-Disubstituted Morpholines**[a]




[a]Isolated yield is shown. In all the cases, dr was determined on the crude reaction mixtures by $^1$H NMR and was found to be ≥19:1.

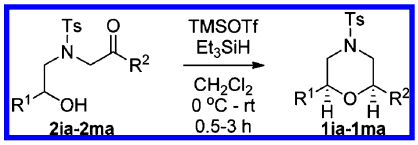
for the synthesis of 2,5-disubstituted morpholines. The keto alcohols **2ba–ea** bearing alkyl or aryl substituents gave the corresponding *cis*-2,5-disubstituted morpholines **1ba–ea** in excellent yield and diastereoselectivity. The thioether moiety was tolerated under these reaction conditions and the morpholine **1ga** was obtained in good yield. Not only the tosyl but even nosyl protection was found to be stable under the reaction conditions employed (cf. morpholine **1fa**). The ester moiety too was unaffected under the reaction conditions, furnishing the morpholine **1ha** in very good yield and diastereoselectivity. It is pertinent to mention here that the morpholine **1ha** was obtained in 98% ee, clearly suggesting that no epimerization of the center $\alpha$ to the ester took place either under basic alkylation conditions or under the influence of the strong Lewis acid used for the reductive etherification. It should be noted that the stereochemistry of the morpholine **1ha** is antipodal to the other cases. The stereochemistry of the morpholine **1ha** was assigned on the basis of single-crystal X-ray diffraction studies.[10] In the other cases, the stereochemistry was assigned by analogy to this example and by comparison with the literature report (for the *trans* isomer of the morpholine **1bb**[5h]).

Table 1 outlines the utility of this reductive etherification based strategy for the stereoselective synthesis of *cis*-2,6-disubstituted morpholine derivatives. The required keto alcohols **2ia–ma** were readily prepared from racemic *N*-tosylamino alcohols **3i–m** and $\alpha$-bromo ketones **4a–c**. Both symmetrically and unsymmetrically substituted morpholine derivatives could be prepared in excellent yield and diastereoselectivity (Table 1, entries 1–7).

Benzyl ether as well as the heteroaromatic thiophene moiety were found to be unaffected under the reaction conditions used (Table 1, entries 5 and 6). For the keto alcohol **2ma**, the reaction furnished the morpholine **1ma** as the only detectable product, and none of the oxazepine formation was observed (Table 1, entry 7). The *cis* stereochemistry of the 2,6-substitutents was ascertained on the basis of the NOE experiments and by comparison with literature data (for morpholine **1jb**[6] and for *trans* isomer of **1ja**[5g]).

We envisioned that synthesis of morpholine moiety fused to a cyclic system will further enhance the utility of the present strategy. Thus, reaction of the keto alcohol **2na** under optimized conditions yielded the morpholine **1na** in good yield and excellent diastereoselectivity (Scheme 4). Similarly, when the keto alcohol **2oa** derived from the *cis*-amino alcohol moiety was subjected to reductive etherification reaction, the morpholine **1oa** was obtained in comparable yield with good diastereoselectivity. The reactions of keto alcohols **2pa–2ra** bearing either a five-membered ring or an eight-membered ring

**Table 1. Stereoselective Synthesis of *cis*-2,6-Disubstituted Morpholines**




| entry | $R^1$ | $R^2$ | | product | yield[a,b] (%) |
|---|---|---|---|---|---|
| 1 | Me | Me | **2ia** | **1ia** | 82 |
| 2 | Ph | Ph | **2jb** | **1jb** | 80 |
| 3 | Ph | Me | **2ja** | **1ja** | 86 |
| 4 | Cy | Me | **2ka** | **1ka** | 92 |
| 5 | $BnOCH_2$ | Me | **2la** | **1la** | 70 |
| 6 | Me | thiophene-2-yl | **2ic** | **1ic** | 72 |
| 7 | $CH_2OH$ | Me | **2ma** | **1ma** | 92 |

[a]Isolated yield. [b]In all cases, dr was determined on the crude reaction mixtures by $^1$H NMR and was found to be ≥19:1.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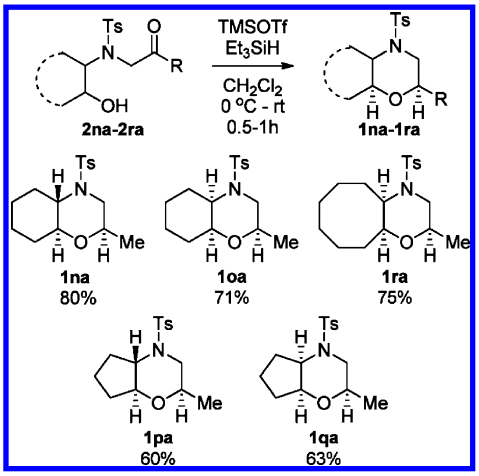
**Scheme 4. Stereoselective Synthesis of Fused Bicyclic Morpholines**[a−c]

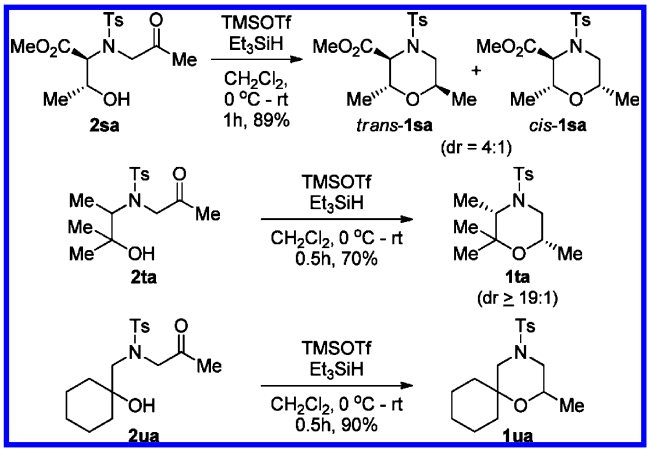



[a]Isolated yield. [b]In all cases, dr was determined on the crude reaction mixtures by $^1$H NMR and was found to be ≥19:1. [c]All products are racemic.

were uneventful, and the corresponding morpholines **1pa−ra** were formed in good to excellent yield.

The strategy was also extended to the synthesis of other C-substituted morpholines. When the keto alcohol **2sa** was subjected to reductive etherification reaction, the 2,3,6-trisubstituted morpholine **1sa** was formed in excellent yield but only with moderate diastereoselectivity (ca. 4:1) favoring *trans* stereochemistry for 2,6-substitution (Scheme 5). The keto

**Scheme 5. Synthesis of 2,3,6-Tri-, 2,2,3,6-Tetrasubstituted, and Spirocyclic Morpholines**




alcohol **2ta** bearing tertiary alcohol moiety yielded the corresponding 2,2,3,6-tetrasubstituted morpholine derivative **1ta** in good yield and excellent diastereoselectivity. Even spirocyclic morpholine **1ua** could be prepared from keto alcohol **2ua** in excellent yield.

The stereochemical outcome of these reactions is dependent on the conformational stability of the oxocarbenium ion intermediate. The tosyl substitution on nitrogen prefers to be in the equatorial orientation (Figure 2). In the case of 2,6-disubstituted morpholines ($R^1$ = alkyl, $R^2$ = H), the alkyl group occupies the pseudoequatorial position. On the contrary, in the case of 2,5-disubstituted morpholine ($R^1$ = H, $R^2$ = alkyl), the alkyl substitution prefers to be in the axial direction perhaps to

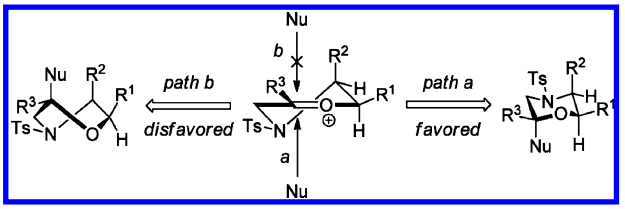
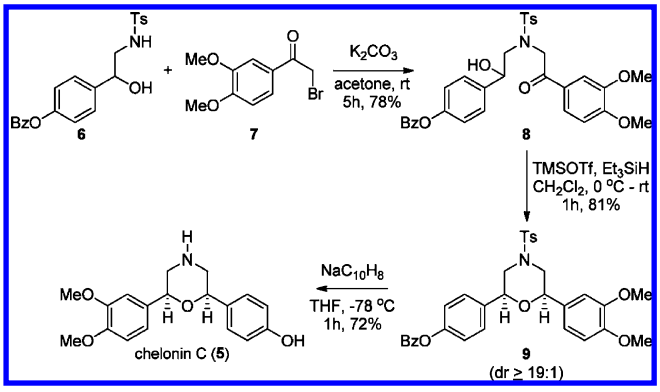



**Figure 2.** Origin of stereoselectivity for substituted morpholines.

avoid interaction with tosyl group. In both the cases, the nucleophile traps the oxocarbenium from the axial direction to lead to chair rather than the twist-boat conformation as proposed by Woerpel in the tetrahydropyran systems, thus resulting in the *cis* stereochemistry of the product.[11] Finally, for the morpholine **1sa**, in the major conformer of the oxocarbenium ion, both the alkyl groups ($R^1$ and $R^2$) would occupy pseudoaxial orientation[4a] and thus lead to the *trans*-**1sa** as the major product, albeit with diminished stereoselectivity.

After successfully demonstrating the scope of the strategy, we turned our attention to applying this strategy for the total synthesis of *rac*-chelonin C (**5**). Chelonin C (**5**) belongs to the family of 2,6-disubstituted morpholines and was isolated from the marine sponge *Chelonaplysilla* sp.[12] This family of alkaloids have been reported to exhibit antimicrobial activity against *Bacillus subtilis* and in vivo anti-inflammatory activity. The synthesis began with the alkylation of the amino alcohol **6** with the bromide **7** to furnish the keto-alcohol **8**. The keto alcohol **8** under reductive etherification conditions furnished the protected chelonin C **9** in 81% yield and with excellent *cis* diastereoselectivity (Scheme 6). Deprotection of tosyl and benzoate groups

**Scheme 6. Stereoselective Synthesis of Chelonin C**




was accomplished in the same pot on treatment with sodium napthalide to give *rac*-chelonin C (**5**) in good yield. The data for the synthetic chelonin C was found to be in good agreement with that reported for natural product. This constitutes the stereoselective, first total synthesis of *rac*-chelonin C (**5**).

In conclusion, we have developed a new reductive etherification-based strategy for the synthesis of diversely substituted morpholines. 2-Substituted, *cis*-2,5-disubstituted, *cis*-2,6-disubstituted, 2,3,6-trisubstituted, 2,2,3,6-tetrasubstituted, bicyclic, and spirocyclic morpholines were prepared with good yields and excellent diastereoselectivities by utilizing this strategy. The noted feature of this approach is that only one of the amino alcohol starting material needs to be prepared in enantiopure form. The developed strategy was also successfully applied in the stereoselective first total synthesis of marine natural product chelonin C.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## EXPERIMENTAL SECTION

**General Materials and Methods.** $^1$H and $^{13}$C NMR spectra were recorded using $CDCl_3$ and $C_6D_6$ as solvents on a 400 MHz spectrometer. For $^1$H NMR spectra, signals arising from the residual proton from the solvent were used as the internal standards. In the $^{13}$C NMR spectra, the nature of the carbons (C/CH/$CH_2$/$CH_3$) was determined by recording the DEPT-135 experiment. Infrared spectra are reported in $cm^{-1}$. Melting points are uncorrected. Dry $CH_2Cl_2$ was prepared by distilling over calcium hydride. All the commercial reagents were used as such without further purification.

**Typical Procedure for Reductive Etherification.** *(2S,5S)-2,5-Dimethyl-4-tosylmorpholine (**1ba**).* To a magnetically stirred solution of keto alcohol **2ba** (155 mg, 0.544 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C were added successively $Et_3SiH$ (95 μL, 0.598 mmol) and TMSOTf (108 μL, 0.598 mmol), and the reaction mixture was allowed to warm to rt. After complete consumption of starting material (TLC control), the reaction mixture was quenched with saturated $NaHCO_3$, extracted with $CH_2Cl_2$, washed with brine, and dried (anhyd $Na_2SO_4$). Evaporation of solvent and purification of residue on silica gel column using EtOAc–hexanes (1:24) as eluent furnished morpholine **1ba** (114 mg, 78%) as a colorless solid: mp 58–60 °C; $[\alpha]^{23}_D$ 46.2 (*c* 1.00, $CHCl_3$); IR (KBr) 2982, 2920, 2899, 2861, 1595, 1489, 1447, 1387, 1377, 1340, 1296, 1280, 1184, 1162, 1112, 1053, 1001, 903, 861, 823, 769, 709 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.00–3.90 (m, 1H), 3.63 (ABX, *J* = 11.2, 2.7 Hz, 1H), 3.59 (ABX, *J* = 11.2, 0.7 Hz, 1H), 3.52 (ABX, *J* = 12.7, 2.8 Hz, 1H), 3.50–3.40 (m, 1H), 2.77 (ABX, *J* = 12.7, 10.6 Hz, 1H), 2.42 (s, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.5 (C), 137.7 (C), 129.9 (2CH), 127.2 (2CH), 72.0 (CH), 71.5 ($CH_2$), 48.3 (CH), 45.9 ($CH_2$), 21.6 ($CH_3$), 18.7 ($CH_3$), 13.8 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{13}H_{20}NO_3S$ 270.1164, found 270.1152.

*(2S,5S)-5-Benzyl-2-methyl-4-tosylmorpholine (**1ca**):* colorless solid; yield 91%; mp 90–92 °C; $[\alpha]^{23}_D$ − 36.6 (*c* 1.00, $CHCl_3$); IR (KBr) 3061, 3026, 2974, 2922, 2866, 1597, 1493, 1455, 1335, 1280, 1153, 1125, 1087, 1050, 1000, 940, 911, 854, 816, 778, 743, 704 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, *J* = 8.2 Hz, 2H), 7.35–7.20 (m, 5H), 7.23 (d, *J* = 8.2 Hz, 2H), 4.10–3.95 (m, 1H), 3.70 (ABX, *J* = 11.8, 0.0 Hz, 1H), 3.63 (ABX, *J* = 13.2, 2.7 Hz, 1H), 3.60–3.50 (m, 1H), 3.47 (ABX, *J* = 11.8, 2.3 Hz, 1H), 3.07 (ABX, *J* = 13.1, 10.5 Hz, 1H), 2.95 (ABX, *J* = 13.2, 10.8 Hz, 1H), 2.73 (ABX, *J* = 13.1, 4.7 Hz, 1H), 2.45 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.5 (C), 138.0 (C), 137.7 (C), 130.0 (2CH), 129.6 (2CH), 128.8 (2CH), 127.2 (2CH), 126.7 (CH), 71.8 (CH), 67.3 ($CH_2$), 54.2 (CH), 46.6 ($CH_2$), 34.1 ($CH_2$), 21.6 ($CH_3$), 18.8 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{19}H_{24}NO_3S$ 346.1477, found 346.1479.

*(2S,5S)-5-Isopropyl-2-methyl-4-tosylmorpholine (**1da**):* colorless liquid; yield 71%; $[\alpha]^{23}_D$ 20.8 (*c* 1.00, $CHCl_3$); IR (neat) 2968, 2924, 2867, 1596, 1455, 1339, 1302, 1277, 1159, 1134, 1092, 1021, 994, 904, 815, 779 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.83 ABX, *J* = 11.4, 0.0 Hz, 1H), 3.60 (ABX, *J* = 14.5, 1.9 Hz, 1H), 3.30–3.20 (m, 2H), 3.20–3.10 (m, 1H), 2.82 (ABX, *J* = 14.5, 11.2 Hz, 1H), 2.42 (s, 3H), 2.30–2.15 (m, 1H), 1.03 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.3 (C), 138.9 (C), 129.9 (2CH), 127.0 (2CH), 70.6 (CH), 66.4 ($CH_2$), 59.0 (CH), 47.1 ($CH_2$), 25.4 ($CH_3$), 21.6 (CH), 20.1 ($CH_3$), 19.9 ($CH_3$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{15}H_{24}NO_3S$ 298.1477, found 298.1462.

*(2S,5S)-5-Methyl-2-phenyl-4-tosylmorpholine (**1bb**):* colorless liquid; yield 77%; $[\alpha]^{23}_D$ 69.5 (c 1.00, $CHCl_3$); IR (neat) 3063, 3033, 2978, 2919, 2864, 1599, 1495, 1450, 1342, 1264, 1161, 1111, 1065, 1034, 979, 912, 869, 816, 733 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (d, *J* = 8.2 Hz, 2H), 7.30–7.15 (m, 5H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.33 (dd, *J* = 10.9, 2.8 Hz, 1H), 4.05–3.95 (m, 1H), 3.75 (ABX, *J* = 11.4, 2.3 Hz, 1H), 3.70 (ABX, *J* = 11.4, 0.0 Hz, 1H), 3.65 (ABX, *J* = 12.5, 2.9 Hz, 1H), 2.92 (ABX, *J* = 12.5, 12.5 Hz, 1H), 2.34 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.6 (C), 139.0 (C), 137.6 (C), 130.0 (2CH), 128.7 (2CH), 128.4 (CH), 127.2 (2CH), 126.1 (2CH), 78.0 (CH), 71.8 ($CH_2$), 48.3 (CH), 46.2 ($CH_2$), 21.6 ($CH_3$), 13.8 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1318.

*(2S,5S)-2-Methyl-5-phenyl-4-tosylmorpholine (**1ea**):* colorless liquid; yield 70%; $[\alpha]^{23}_D$ 58.4 (c 1.00, $CHCl_3$); IR (neat) 3058, 2979, 2919, 2865, 1599, 1495, 1451, 1381, 1341, 1299, 1268, 1162, 1120, 1096, 1022, 997, 907, 843, 816, 770, 737, 703 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, *J* = 8.2 Hz, 2H), 7.45–7.40 (m, 2H), 7.30–7.20 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.89 (dd, *J* = 3.4, 0.0 Hz, 1H), 4.25 (ABX, *J* = 12.0, 0.0 Hz, 1H), 3.78 (ABX, *J* = 12.0, 3.7 Hz, 1H), 3.57 (ABX, *J* = 13.8, 2.5 Hz, 1H), 3.55–3.40 (m, 1H), 2.80 (ABX, *J* = 13.8, 10.9 Hz, 1H), 2.38 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.4 (C), 138.0 (C), 137.7 (C), 129.8 (2CH), 128.5 (2CH), 128.4 (2CH), 127.7 (CH), 127.2 (2CH), 71.4 (CH), 69.0 ($CH_2$), 54.4 (CH), 47.1 ($CH_2$), 21.6 ($CH_3$), 18.8 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1308.

*(2S,5S)-5-Benzyl-2-methyl-4-tosylmorpholine (**1fa**):* colorless liquid; yield 85%; $[\alpha]^{24}_D$ 71.0 (*c* 0.3, $CHCl_3$); IR (neat) 3028, 2975, 2927, 2863, 1590, 1544, 1452, 1368, 1346, 1276, 1167, 1124, 1058, 999, 941, 909, 854, 777, 740, 702 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, *J* = 7.6 Hz, 1H), 7.70–7.55 (m, 3H), 7.25–7.10 (m, 5H), 3.95–3.85 (m, 1H), 3.74 (ABX, *J* = 11.2, 0.0 Hz, 1H), 3.63 (ABX, *J* = 13.4, 2.5 Hz, 1H), 3.60–3.50 (m, 2H), 3.17 (ABX, *J* = 9.8, 5.2 Hz, 1H), 3.13 (ABX, *J* = 11.2, 5.8 Hz, 1H), 2.92 (ABX, *J* = 13.1, 5.2 Hz, 1H), 1.24 (d, *J* = 6.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 147.6 (C), 137.7 (C), 133.8 (C), 133.6 (CH), 132.2 (CH), 131.0 (CH), 129.6 (2CH), 128.7 (2CH), 126.8 (CH), 124.6 (CH), 72.4 (CH), 67.6 ($CH_2$), 55.2 (CH), 47.1 ($CH_2$), 35.2 ($CH_2$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{18}H_{21}N_2O_5S$ 377.1171, found 377.1165.

*(2S,5S)-2-Methyl-5-(2-(methylthio)ethyl)-4-tosylmorpholine (**1ga**):* colorless liquid; yield 75%; $[\alpha]^{23}_D$ 43.5 (*c* 1.00, $CHCl_3$); IR (neat) 3034, 2971, 2920, 2862, 1598, 1493, 1449, 1339, 1303, 1277, 1214, 1160, 1117, 1042, 997, 907, 814, 733 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 3.87 (td, *J* = 7.3, 2.8 Hz, 1H), 3.65 (ABX, *J* = 11.4, 0.0 Hz, 1H), 3.60 (ABX, *J* = 13.8, 2.8 Hz, 1H), 3.43 (ABX, *J* = 11.8, 2.6 Hz, 1H), 3.35–3.25 (m, 1H), 2.82 (ABX, *J* = 13.8, 11.4 Hz, 1H), 2.50–2.40 (m, 2H), 2.42 (s, 3H), 2.05 (s, 3H),1.95–1.80 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.6 (C), 138.2 (C), 130.0 (2CH), 127.1 (2CH), 71.2 (CH), 68.5 ($CH_2$), 51.7 (CH), 46.6 ($CH_2$), 30.9 ($CH_2$), 27.7 ($CH_2$), 21.6 ($CH_3$), 18.7 ($CH_3$), 15.5 ($CH_3$); HRMS (ESI, Ms + $H^+$) *m*/*z* calcd for $C_{15}H_{24}NO_3S_2$ 330.1198, found 330.1201.

*(3S,6R)-Methyl 6-methyl-4-tosylmorpholine-3-carboxylate (**1ha**):* colorless solid; yield 88%; mp 106–108 °C; $[\alpha]^{23}_D$ − 57.6 (*c* 1.00, $CHCl_3$); IR (KBr) 2984, 2971, 2925, 2867, 1750, 1597, 1445, 1344, 1301, 1279, 1213, 1166, 1110, 1094, 1047, 1009, 918, 826, 755 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.51 (d, *J* = 2.2 Hz, 1H), 4.31 (ABX, *J* = 11.6, 0.0 Hz, 1H), 3.77 (ABX, *J* = 11.6, 3.3 Hz, 1H), 3.60–3.50 (m, 2H), 3.56 (s, 3H), 3.03 (ABX, *J* = 12.0, 12.0 Hz, 1H), 2.43 (s, 3H), 1.13 (d, *J* = 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.6 (CO), 143.7 (C), 136.6 (C), 129.7 (2CH), 127.4 (2CH), 72.4 (CH), 69.0 ($CH_2$), 54.6 (CH), 52.4 ($CH_3$), 47.6 ($CH_2$), 21.7 ($CH_3$), 18.6 ($CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{14}H_{20}NO_5S$ 314.1062, found 314.1052.

*(2S*,6R*)-2,6-Dimethyl-4-tosylmorpholine (**1ia**):* colorless solid; yield 82%; mp 100–102 °C; IR (KBr) 2974, 2931, 2888, 2845, 1599, 1493, 1457, 1380, 1347, 1327, 1300, 1238, 1166, 1137, 1085, 1005, 944, 907, 843, 809, 782 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 3.75–3.60 (m, 2H), 3.54 (ABX, *J* = 10.7, 0.0 Hz, 2H), 2.43 (s, 3H), 1.91 (ABX, *J* = 10.7, 10.7 Hz, 2H), 1.12 (d, *J* = 6.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.0 (C), 132.3 (C), 129.9 (2CH), 127.9 (2CH), 71.4 (2CH), 51.0 ($2CH_2$), 21.7 ($CH_3$), 18.8 ($2CH_3$); HRMS (ESI, M + $H^+$) *m*/*z* calcd for $C_{13}H_{20}NO_3S$ 270.1164, found 270.1165.

*(2S*,6R*)-2-Cyclohexyl-6-methyl-4-tosylmorpholine (**1ka**):* colorless solid; yield 92%; mp 126–128 °C; IR (KBr) 2929, 2849, 1595, 1449, 1343, 1161, 1095, 1064, 994, 932, 816, 774 $cm^{-1}$; $^1$H

NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$ = 8.2 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), 3.70−3.55 (m, 2H), 3.54 (ABX, $J$ = 11.0, 0.0 Hz, 1H), 3.35−3.20 (m, 1H), 2.44 (s, 3H), 1.97 (ABX, $J$ = 11.0, 11.0 Hz, 1H), 1.90 (ABX, $J$ = 10.7, 10.7 Hz, 1H), 1.90−1.80 (m, 1H), 1.75−1.50 (m, 4H), 1.35−1.10 (m, 4H), 1.11 (d, $J$ = 6.2 Hz, 3H), 1.05−0.90 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.9 (C), 132.5 (C), 129.9 (2CH), 127.9 (2CH), 79.5 (CH), 71.4 (CH), 51.4 ($CH_2$), 47.8 ($CH_2$), 41.1 (CH), 29.1 ($CH_2$), 28.6 ($CH_2$), 26.5 ($CH_2$), 26.1 ($CH_2$), 26.0 ($CH_2$), 21.7 ($CH_3$), 18.8 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{18}H_{28}NO_3S$ 338.1790, found 338.1786.

*(2R*,6R*)-2-(Benzyloxymethyl)-6-methyl-4-tosylmorpholine (**1la**):* pale yellow liquid; yield 70%; IR (neat) 3062, 3032, 2978, 2869, 2251, 1724, 1599, 1495, 1453, 1347, 1235, 1166, 1089, 1001, 912, 812, 783, 734, 703 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$ = 8.2 Hz, 2H), 7.40−7.25 (m, 7H), 4.52 (s, 2H), 3.85−3.75 (m, 1H), 3.75−3.65 (m, 1H), 3.64 (ABX, $J$ = 11.0, 2.0 Hz, 1H), 3.56 (ABX, $J$ = 11.0, 2.0 Hz, 1H), 3.48 (ABX, $J$ = 10.2, 5.0 Hz, 1H), 3.40 (ABX, $J$ = 10.2, 5.0 Hz, 1H), 2.44 (s, 3H), 2.12 (ABX, $J$ = 11.0, 11.0 Hz, 1H), 1.96 (ABX, $J$ = 11.0, 11.0 Hz, 1H), 1.15 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.0 (C), 137.9 (C), 132.4 (C), 129.9 (2CH), 128.6 (CH), 128.0 (2CH), 127.9 (2CH), 127.9 (2CH), 74.5 (CH), 73.6 ($CH_2$), 71.7 (CH), 70.6 ($CH_2$), 51.2 ($CH_2$), 47.4 ($CH_2$), 21.7 ($CH_3$), 18.7 ($CH_3$); HRMS (ESI, M + $Na^+$) $m/z$ calcd for $C_{20}H_{25}NO_4NaS$ 398.1402, found 398.1414.

*(2R*,6R*)-2-Methyl-6-(thiophene-2-yl)-4-tosylmorpholine (**1ic**):* colorless liquid; yield 72%; IR (neat) 3107, 3068, 2979, 2874, 2275, 1598, 1493, 1450, 1349, 1234, 1166, 1088, 998, 934, 912, 877, 816, 730 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 8.2 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), $\delta$ 7.25 (dd, $J$ = 4.7, 1.1 Hz, 1H), 7.00−6.90 (m, 2H), 4.91 (dd, $J$ = 10.5, 2.5 Hz, 1H), 3.95−3.85 (m, 1H), 3.84 (ABX, $J$ = 11.2, 2.5 Hz, 1H), 3.64 (ABX, $J$ = 11.2, 2.2 Hz, 1H), 2.44 (s, 3H), 2.31 (ABX, $J$ = 11.2, 10.5 Hz, 1H), 2.08 (ABX, $J$ = 11.2, 10.6 Hz, 1H), 1.22 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.2 (C), 141.4 (C), 132.4 (C), 130.0 (2CH), 127.9 (2CH), 126.8 (CH), 125.3 (CH), 124.7 (CH), 73.8 (CH), 72.2 (CH), 51.4 ($CH_2$), 51.0 ($CH_2$), 21.7 ($CH_3$), 18.8 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{16}H_{20}NO_3S_2$ 338.0885, found 338.0870.

*((2R*,6R*)-6-Methyl-4-tosylmorpholin-2-yl)methanol (**1ma**):* pale yellow liquid; yield 92%; IR (neat) 3502, 2978, 2925, 2877, 1600, 1454, 1341, 1236, 1163, 1090, 1045, 1001, 812, 782 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$ = 8.0 Hz, 2H), 7.34 (d, $J$ = 8.0 Hz, 2H), 3.80−3.70 (m, 2H), 3.68 (ABX, $J$ = 12.0, 2.4 Hz, 1H), 3.57 (ABX, $J$ = 10.6, 0.0 Hz, 2H), 3.52 (ABX, $J$ = 12.0, 4.9 Hz, 1H), 2.44 (s, 3H), 2.17 (ABX, $J$ = 10.6, 10.6 Hz, 1H), 1.94 (ABX, $J$ = 10.6, 10.6 Hz, 1H), 1.15 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.1 (C), 132.2 (C), 130.0 (2CH), 128.0 (2CH), 75.5 (CH), 71.7 (CH), 63.6 ($CH_2$), 51.2 ($CH_2$), 46.4 ($CH_2$), 21.7 ($CH_3$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{13}H_{20}NO_4S$ 286.1113, found 286.1106.

*(2R*,4aS*,8aS*)-2-Methyl-4-tosyloctahydro-2H-benzo[b][1,4]-oxazine (**1na**):* colorless solid; yield 80%; mp 84−86 °C; IR (KBr) 2930, 2851, 2814, 1595, 1455, 1383, 1350, 1162, 1092, 1046, 1015, 902, 865, 810, 767, 705 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$ = 8.2 Hz, 2H), 7.33 (d, $J$ = 8.2 Hz, 2H), 3.88 (ABX, $J$ = 11.6, 2.2 Hz, 1H), 3.85−3.75 (m, 1H), 3.30−3.20 (m, 1H), 2.60−2.50 (m, 1H), 2.44 (s, 3H), 2.31 (ABX, $J$ = 11.6, 10.5 Hz, 1H), 2.17 (ddd, $J$ = 12.0, 8.8, 3.7 Hz, 1H), 1.90−1.80 (m, 1H), 1.80−1.60 (m, 2H), 1.50−1.40 (m, 1H), 1.35−1.20 (m, 2H), 1.15 (d, $J$ = 6.2 Hz, 3H), 1.15−1.05 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.7 (C), 134.7 (C), 129.9 (2CH), 127.6 (2CH), 79.6 (CH), 71.6 (CH), 62.8 (CH), 54.6 ($CH_2$), 31.7 ($CH_2$), 29.5 ($CH_2$), 25.0 ($CH_2$), 24.1 ($CH_2$), 21.7 ($CH_3$), 18.9 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{16}H_{24}NO_3S$ 310.1477, found 310.1483.

*(2R*,4aR*,8aS*)-2-Methyl-4-tosyloctahydro-2H-benzo[b][1,4]-oxazine (**1oa**):* colorless solid; yield 71%; mp 86−88 °C; IR (KBr) 2933, 2862, 1596, 1450, 1376, 1336, 1151, 1104, 1011, 918, 899, 817, 706 $cm^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.76 (d, $J$ = 8.2 Hz, 2H), 6.80 (d, $J$ = 8.2 Hz, 2H), 3.90−3.80 (m, 1H), 3.54 (ABX, $J$ = 12.8, 2.9 Hz, 1H), 3.50−3.40 (m, 1H), 3.40−3.30 (m, 1H), 2.63 (ABX, $J$ = 12.8, 10.8 Hz, 1H), 1.90 (s, 3H), 1.80−1.70 (m, 1H), 1.65 (qd, $J$ = 12.1, 3.3 Hz, 1H), 1.45−1.30 (m, 3H), 1.15−0.90 (m, 3H), 0.86 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 142.7 (C), 139.8 (C), 129.8 (2CH), 127.5 (2CH), 74.3 (CH), 72.0 (CH), 53.9 (CH), 46.1 ($CH_2$), 31.6 ($CH_2$), 24.9 ($CH_2$), 23.4 ($CH_2$), 21.1 ($CH_3$), 19.8 ($CH_2$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{16}H_{24}NO_3S$ 310.1477, found 310.1484.

*(2R*,4aS*,7aS*)-2-Methyl-4-tosyloctahydrocyclopenta[b][1,4]-oxazine (**1pa**):* colorless solid; yield 60%; mp 132−134 °C; IR (KBr) 2967, 2927, 2876, 1599, 1453, 1400, 1380, 1335, 1308, 1289, 1166, 1123, 1092, 1042, 927, 871, 814, 783, 709 $cm^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.66 (d, $J$ = 8.2 Hz, 2H), 6.81 (d, $J$ = 8.2 Hz, 2H), 3.72 (ABX, $J$ = 11.4, 2.4 Hz, 1H), 3.60−3.50 (m, 1H), 3.35−3.25 (m, 1H), 2.25−2.20 (m, 1H), 2.10−1.90 (m, 3H), 1.91 (s, 3H), 1.65−1.55 (m, 1H), 1.40−1.15 (m, 3H), 0.87 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 143.3 (C), 133.4 (C), 129.7 (2CH), 128.4 (2CH), 83.0 (CH), 72.8 (CH), 62.0 (CH), 54.0 ($CH_2$), 27.1 ($CH_2$), 25.7 ($CH_2$), 21.2 ($CH_3$), 18.4 ($CH_3$), 17.6 ($CH_2$); HRMS (ESI, M + $Na^+$): $m/z$ calcd for $C_{15}H_{21}NO_3NaS$ 318.1140, found 318.1150.

*(2R*,4aR*,7aS*)-2-Methyl-4-tosyloctahydrocyclopenta[b][1,4]-oxazine (**1qa**):* colorless liquid; yield 63%; IR (neat) 2974, 2876, 1599, 1454, 1342, 1267, 1158, 1123, 1092, 1060, 1034, 1000, 927, 872, 816, 737, 706 $cm^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.73 (d, $J$ = 8.2 Hz, 2H), 6.80 (d, $J$ = 8.2 Hz, 2H), 4.02 (td, $J$ = 9.6, 3.6 Hz, 1H), 3.60−3.50 (m, 2H), 3.30−3.20 (m, 1H), 2.42 (ABX, $J$ = 12.0, 10.7 Hz, 1H), 1.91 (s, 3H), 1.60−1.45 (m, 2H), 1.40−1.30 (m, 2H), 1.30−1.10 (m, 2H), 0.82 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 142.8 (C), 138.3 (C), 129.7 (2CH), 127.8 (2CH), 78.1 (CH), 70.8 (CH), 56.6 (CH), 45.8 ($CH_2$), 29.8 ($CH_2$), 22.0 ($CH_2$), 21.2 ($CH_3$), 21.0 ($CH_2$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{15}H_{22}NO_3S$ 296.1320, found 296.1333.

*(2R*,4aR*,10aS*)-2-Methyl-4-tosyldecahydro-2H-cycloocta[b]-[1,4]oxazine (**1ra**):* colorless liquid; yield 75%; IR (neat) 3057, 2927, 2860, 1599, 1448, 1373, 1338, 1268, 1222, 1161, 1118, 1090, 1061, 1020, 924, 893, 861, 813, 738, 707 $cm^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 7.76 (d, $J$ = 8.2 Hz, 2H), 6.81 (d, $J$ = 8.2 Hz, 2H), 4.20−4.15 (m, 1H), 3.59 (ABX, $J$ = 12.4, 2.8 Hz, 1H), 3.55−3.35 (m, 2H), 2.43 (ABX, $J$ = 12.4, 10.7 Hz, 1H), 1.90 (s, 3H), 1.90−1.75 (m, 1H), 1.65−1.00 (m, 12H), 0.88 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 142.8 (C), 139.3 (C), 129.7 (2CH), 127.5 (2CH), 78.8 (CH), 71.9 (CH), 55.0 (CH), 46.6 ($CH_2$), 28.7 ($CH_2$), 28.5 ($CH_2$), 26.9 ($CH_2$), 25.7 ($CH_2$), 24.6 ($CH_2$), 21.5 ($CH_2$), 21.1 ($CH_3$), 18.7 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{18}H_{28}NO_3S$ 338.1790, found 338.1781.

*(2R,3S,6S)-Methyl 2,6-dimethyl-4-tosylmorpholine-3-carboxylate (cis-**1sa**):* colorless liquid; yield 18%; $[\alpha]^{23}_D$ −98.4 (c 1.00, $CHCl_3$); IR (neat) 2981, 2927, 2899, 2854, 1744, 1596, 1492, 1449, 1354, 1278, 1202, 1167, 1139, 1116, 1033, 972, 906, 869, 813 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 8.2 Hz, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 3.86 (s, 3H), 3.85−3.70 (m, 2H), 3.53 (ABX, $J$ = 11.0, 2.5 Hz, 1H), 2.85 (d, $J$ = 9.0 Hz, 1H), 2.46 (s, 3H), 1.94 (ABX, $J$ = 11.0, 11.0 Hz, 1H), 1.13 (d, $J$ = 6.3 Hz, 3H), 1.12 (d, $J$ = 6.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.1 (CO), 144.7 (C), 130.7 (C), 130.0 (2CH), 128.9 (2CH), 74.1 (CH), 71.0 (CH), 64.4 (CH), 53.0 ($CH_3$), 51.0 ($CH_2$), 21.8 ($CH_3$), 18.8 ($CH_3$), 18.0 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{15}H_{22}NO_5S$ 328.1219, found 328.1231.

*(2R,3S,6R)-Methyl 2,6-dimethyl-4-tosylmorpholine-3-carboxylate (trans-**1sa**):* colorless solid; 71%; mp 96−98 °C; $[\alpha]^{23}_D$ − 39.4 (*c* 1.00, $CHCl_3$); IR (KBr) 2982, 2954, 2933, 1747, 1598, 1451, 1343, 1285, 1164, 1121, 1091, 1040, 1011, 910, 814, 734 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.2 Hz, 2H), 7.29 (d, $J$ = 8.2 Hz, 2H), 4.53 (q, $J$ = 6.6 Hz, 1H), 4.29 (s, 1H), 4.05−3.90 (m, 1H), 3.54 (s, 3H), 3.52 (ABX, $J$ = 12.4, 3.1 Hz, 1H), 2.99 (ABX, $J$ = 12.4, 11.0 Hz, 1H), 2.42 (s, 3H), 1.46 (d, $J$ = 6.7 Hz, 3H), 1.06 (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.9 (CO), 143.6 (C), 136.6 (C), 129.6 (2CH), 127.4 (2CH), 70.4 (CH), 63.1 (CH), 58.2 (CH), 52.4 ($CH_3$), 47.3 ($CH_2$), 21.7 ($CH_3$), 18.7 ($CH_3$), 16.9 ($CH_3$); HRMS (ESI, M + $H^+$) $m/z$ calcd for $C_{15}H_{22}NO_5S$ 328.1219, found 328.1231.

*(3S*,6S*)-2,2,3,6-Tetramethyl-4-tosylmorpholine (**1ta**):* colorless solid; yield 70%; mp 72−74 °C; IR (KBr) 2984, 2928, 1597, 1449, 1381, 1334, 1277, 1244, 1154, 1086, 1056, 1000, 924, 882, 843, 814, 752, 707 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.2 Hz, 2H), 7.29 (d, $J$ = 8.2 Hz, 2H), 3.95−3.85 (m, 1H), 3.67 (q, $J$ = 6.6 Hz,

1H), 3.45 (ABX, $J$ = 12.4, 3.5 Hz, 1H), 2.60 (ABX, $J$ = 12.4, 11.3 Hz, 1H), 2.42 (s, 3H), 1.35 (s, 3H), 1.10 (d, $J$ = 6.6 Hz, 3H), 1.09 (s, 3H), 0.92 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.3 (C), 137.8 (C), 129.9 (2CH), 127.1 (2CH), 74.1 (C), 65.0 (CH), 54.5 (CH), 44.8 ($CH_2$), 26.6 ($CH_3$), 23.7 ($CH_3$), 21.7 ($CH_3$), 19.1 ($CH_3$), 10.8 ($CH_3$); HRMS (ESI, M + H$^+$) $m/z$ calcd for $C_{15}H_{24}NO_3S$ 298.1477, found 298.1464.

*(RS)-2-Methyl-4-tosyl-1-oxa-4-azaspiro[5.5]undecane (**1ua**):* colorless liquid; yield 90%; IR (neat) 3058, 2931, 2857, 1599, 1492, 1452, 1344, 1306, 1270, 1215, 1163, 1087, 1049, 1018, 987, 937, 903, 846, 815, 738 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 7.6 Hz, 2H), 7.32 (d, $J$ = 7.6 Hz, 2H), 3.95−3.90 (m, 1H), 3.54 (ABX, $J$ = 11.0, 0.0 Hz, 1H), 3.50 (AB, $J$ = 11.2 Hz, 1H), 2.43 (s, 3H), 2.05−2.00 (m, 1H), 1.92 (AB, $J$ = 11.2 Hz, 1H), 1.86 (ABX, $J$ = 11.0, 11.0 Hz, 1H), 1.70−1.20 (m, 9H), 1.06 (d, $J$ = 5.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.8 (C), 132.7 (C), 129.8 (2CH), 127.8 (2CH), 72.4 (C), 63.8 (CH), 53.1 ($CH_2$), 51.8 ($CH_2$), 36.9 ($CH_2$), 29.7 ($CH_2$), 26.1 ($CH_2$), 21.7 ($CH_3$), 21.6 ($CH_2$), 21.5 ($CH_2$), 19.2 ($CH_3$); HRMS (ESI, M + H$^+$) $m/z$ calcd for $C_{17}H_{26}NO_3S$ 324.1633, found 324.1631.

*4-((2R*,6S*)-6-(3,4-Dimethoxyphenyl)-4-tosylmorpholin-2-yl)-phenyl Benzoate (**9**).* To a stirred solution of amino alcohol **6** (195 mg, 0.474 mmol) in acetone were added successively $K_2CO_3$ (131 mg, 0.948 mmol) and bromide **7** (134 mg, 0.521 mmol), and the resulting mixture was stirred at rt for 5 h (TLC control). The reaction mixture was filtered through Celite, concentrated in vacuo, and purified by silica gel column chromatography using EtOAc−hexanes (1:4) as eluent to furnish keto alcohol **8** (220 mg, 78%) as a colorless solid. Reaction of keto alcohol **8** (200 mg, 0.340 mmol) with $Et_3SiH$ (60 $\mu$L, 0.374 mmol) and TMSOTf (68 $\mu$L, 0.374 mmol) in $CH_2Cl_2$ (5 mL), as described for the morpholine **1ba**, followed by purification on silica gel column using EtOAc−hexanes (1:6) as eluent furnished morpholine **9** (158 mg, 81%) as a colorless solid: mp 184−186 °C; IR (KBr) 3064, 3001, 2959, 2930, 2845, 1736, 1600, 1513, 1450, 1347, 1264, 1203, 1166, 1085, 1025, 984, 825, 737, 710 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.0 Hz, 2H), 7.65 (t, $J$ = 7.4 Hz, 1H), 7.61 (d, $J$ = 8.1 Hz, 2H), 7.52 (t, $J$ = 7.7 Hz, 2H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 8.4 Hz, 2H), 6.97 (d, $J$ = 8.3 Hz, 1H), 6.91 (s, 1H), 6.86 (d, $J$ = 8.3 Hz, 1H), 4.88 (d, $J$ = 8.4 Hz, 1H), 4.81 (d, $J$ = 8.4 Hz, 1H), 4.00−3.85 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.43 (s, 3H), 2.27 (td, $J$ = 11.5, 2.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.3 (CO), 150.9 (C), 149.2 (2C), 144.2 (C), 136.4 (C), 133.9 (CH), 132.3 (C), 131.3 (C), 130.3 (2CH), 130.0 (2CH), 129.5 (C), 128.8 (2CH), 128.0 (2CH), 127.4 (2CH), 122.0 (2CH), 118.5 (CH), 111.3 (CH), 109.6 (CH), 77.6 (CH), 77.2 (CH), 56.2 ($CH_2$), 56.1 ($CH_2$), 51.8 ($2CH_3$), 21.7 ($CH_3$); HRMS (ESI, M + H$^+$) $m/z$ calcd for $C_{32}H_{32}NO_7S$ 574.1899, found 574.1876.

*rac-Chelonin C (**5**).* To a cold (−78 °C) solution of compound **9** (105 mg, 0.183 mmol) in dry THF (4 mL) was added sodium naphthalide solution [prepared by adding naphthalene (178 mg, 1.373 mmol) to sodium (25.2 mg, 1.098 mmol) in dry THF (3 mL) at rt and stirred for 2 h] and the resulting solution stirred for 1 h. The reaction mixture was quenched by addition of saturated $NH_4Cl$ at −78 °C and warmed to rt. The reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layer was washed with dilute HCl (3 × 5 mL). The aqueous layer was neutralized with saturated aq $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine, dried (anhyd $Na_2SO_4$), and evaporated to furnish chelonin C (**5**) (42 mg, 72%) as a colorless solid: mp 136−138 °C; IR (KBr) 3441, 3287, 2952, 2917, 2845, 1731, 1609, 1517, 1460, 1416, 1262, 1160, 1139, 1089, 1024, 913, 835, 813, 764 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$) 7.25 (d, $J$ = 8.4 Hz, 2H), 7.02 (s, 1H), 6.97 (d, $J$ = 8.3 Hz, 1H), 6.92 (d, $J$ = 8.2 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 2H), 4.60 (t, $J$ = 10.2 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.99 (t, $J$ = 11.8 Hz, 2H, 2H), 2.80−2.65 (m, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 158.3 (C), 150.4 (C), 150.1 (C), 134.6 (C), 132.5 (C), 128.6 (2CH), 119.8 (CH), 116.1 (2CH), 112.8 (CH), 111.3 (CH), 80.2 (CH), 80.2 (CH), 56.5 ($2CH_3$), 52.7 ($CH_2$), 52.7 ($CH_2$); HRMS (ESI, M + H$^+$) $m/z$ calcd for $C_{18}H_{22}NO_4$ 316.1549, found 316.1551.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Spectroscopic data ($^1$H NMR, $^{13}$C NMR and NOE's) of all the products and HPLC chromatogram for the compound **1ha**. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ DEDICATION

Dedicated to Professor V. K. Singh, IIT Bombay, on the occasion of his 60th birthday.

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