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The Combination of Diallylboration and Ring-Closing Metathesis in the Synthesis of Spiro-β-Amino Alcohols and (±)-Cephalotaxine

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A convenient and practical methodology for the preparation of various spiro-β-amino alcohols has been elaborated. The approach involves allylboration and ring-closing methathesis to prepare spirobicyclic compounds and their subsequent modification to spiro-β-amino alcohols containing four- to six-membered azacycles. *N*-Boc-protected azaspirocyclic olefins reacted with NBS in solvent under reflux to give tricyclic bromocyclocarbamates. The structure of one of the bromides was established by single-crystal X-ray analysis. The dehydrobromination of the tricyclic bromides with *t*BuOK produced olefins in good yields, which underwent allylic-type rearrangement in the presence of $MgBr_2{\cdot}Et_2O$. Alkaline hydrolysis of the rearranged carbamates led to diastereomerically pure spiro-β-amino alcohols. The structure of the dimethyl-substituted amino alcohol was proved by single-crystal X-ray analysis. *rac*-(5*R**,6*S**)-1-Azaspiro[4.4]non-7-en-6-ol was used in the formal synthesis of cephalotaxine.

Introduction

The family of Cephalotaxus alkaloids has attracted considerable attention since their first isolation in 1963.[1] Many works devoted to the preparation of cephalotaxine (CPT) and its close analogues can be found in the literature.[2] The interest shown by synthetic chemists in its synthesis can be attributed to two main reasons. First, CPT (Figure 1) possesses a unique pentacyclic skeleton that contains a 1-azaspiro[4.4]nonane unit, which serves as a useful model for the development of new approaches to azaspiranes. Secondly, the esters of CPT, harringtonines, are the main components of drugs used to cure several types of human leukemia (passing the third phase of clinical trials) and have also been investigated for application in the treatment of chloroquine-resistant malaria.[3] Despite the relatively simple structure of CPT, the construction of the azaspiro fragment is a somewhat challenging task,[2] whereas other steps of the CPT synthesis are well established.

Recently we have demonstrated the utility of the diallylboration and ring-closure metathesis (RCM) sequence in the preparation of various spiro[4a] and bridged[4b,4c] azabicycles starting from aromatic heterocycles (pyridines, isoquinolines, and pyrrole) and lactams. Having such a straightforward access to azaspirobicycles we decided to develop the synthesis of CPT. Our first attempt to use the Heck-type reaction to form the azepine cycle of CPT resulted in a novel eight-membered cyclization that led to a structural isomer of the main pentacyclic core of CPT.[5] However, this approach was unsuitable for CPT preparation. Accordingly we concentrated our attention on the modification of the spirobicycles to give products that have already found application in the synthesis of CPT.

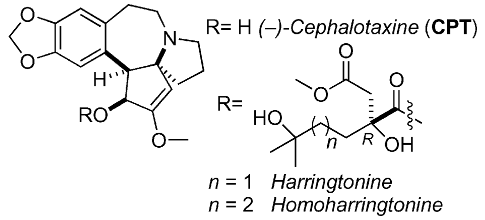

Figure 1. Cephalotaxus alkaloids.

Isono and Mori[2l] have shown that the azepine cycle of CPT can be formed by electrophilic cyclization under the action of polyphosphoric acid (PPA) on a mixture of diastereomeric allylic-type spiro-β-amino alcohols. Moreover, some spiro-β- and -γ-amino alcohols or their parent ketones are very interesting compounds because they serve as intermediates in a number of syntheses of natural products, such as histrionicotoxine,[6a] sibirine,[6b] halichlorine,[6c,6f] fasicularine,[6d,6e] and pinnaic acid.[6f] Therefore the elaboration of new and practical methods to this type of compound is an important task. This report reveals a route to the spiro-β-amino alcohols of the azaspiro[4,*n*]nonene series.

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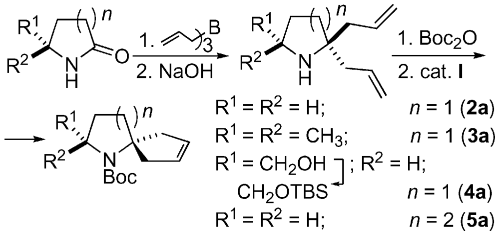
Results and Discussion

We first prepared a set of spiranes by our conventional approach. The spirane **1a** with a four-membered aza ring was prepared from 3-chloropropionitrile (Scheme 1).

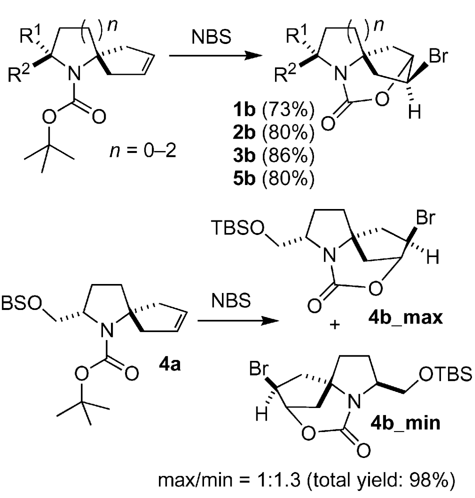
The diallylboration of nitriles[7a,7b] with triallylborane (TAB) was carried out by heating at 110 °C and proceeded via the formation of diazadiboretidines, which after alkaline treatment released diallylated primary amines. In the case of 3-chloropropionitrile, diallylboration followed by deboronation of the reaction mixture with NaOH liberated the 2,2-diallylazetidine (Scheme 1) in 91% yield in a one-pot reaction. Protection of 2,2-diallylazetidine with Boc_2O followed by RCM (Grubbs' catalyst **I**, 1.3 mol-%) provided spirocycle **1a**. Spiranes with a five- (**2a**–**4a**) or six-membered (**5a**) aza ring were prepared from lactams[4a] (Scheme 2). The lactams readily reacted with TAB in THF or benzene solution under reflux to give 2,2-diallylated heterocycles after alkaline treatment.[7c] Further protection of the amino function and RCM furnished the required spiranes **2a**–**5a**. Bicycle **4a** was prepared in an enantiomerically pure form starting from (*S*)-2-(hydroxymethyl)pyrrolidone. The *N*-Boc-protected diallylated precursor of **4a** was subjected to RCM (catalyst **I**, 2.0 mol-%) without protection of the OH group to give a crystalline product (85%).



Scheme 2. Synthesis of pyrrolidine- and piperidine-type spiranes.

The protected azaspiro-olefins **1a**–**5a** were modified by intramolecular bromocyclocarbamation using NBS (Scheme 3).

Halocyclization is a common approach to the stereoselective introduction of hydroxy or amino groups into molecules.[8] However, spiro systems have not been modified this way previously as the reaction requires rather harsh conditions, with the exception of the six-membered spirane **5a**; the tricyclic bromide **5b** (80%) was formed at room temperature. Bicycles with contracted rings, **2a**–**4a**, upon heating under reflux in $CHCl_3$ with NBS produced tricyclic bromides **2b** (80%), **3b** (86%), and **4b** (mixture of diastereomers, 98%), respectively. The structure of **2b** was established by single-crystal X-ray analysis (Figure 2).



Scheme 3. Modification of **1a**–**5a** with NBS.

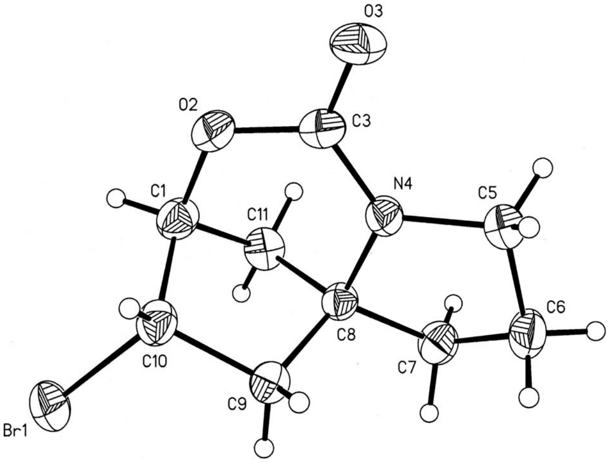
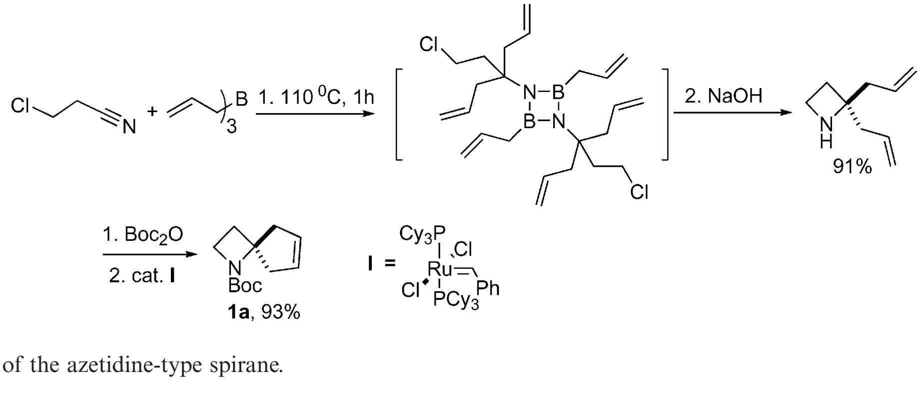


Figure 2. Molecular structure of **2b**.

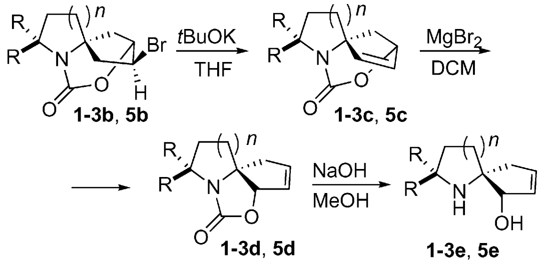
The reaction of **1a** (DCE at reflux) proved the most difficult and was accompanied by partial decomposition of the substrate, which reduced the yield of **1b** (73%). This observation can be rationalized by taking into account the strained nature of the azetedine ring in the tricyclic system.



Scheme 1. Synthesis of the azetidine-type spirane.

Note that an α substituent, even a bulky TBS group as in **4a**, has little effect on the diastereoselectivity of the bromocyclization due to the coplanarity of the amidic carbonyl group; its deviation from the plane of the pyrrolidine cycle is 1.80° (X-ray data of **2b**). The diastereoisomers **4b_min** and **4b_max** obtained from the reaction with NBS in MeCN were separated by flash chromatography and their structures were assigned by NMR experiments.

The bromides **1b**–**5b** were subjected to a dehydrobromination reaction. Previously, DBU was used in a test reaction with **2b**, however, prolonged reaction times even with an excess of DBU and the formation of a mixture of products makes it unsuitable for the dehydrobromination step. Fortunately, we found that the dehydrobromination proceeded smoothly under the action of *t*BuOK in THF giving rise to spiro-olefin **2c** in 93% yield (Scheme 4, Table 1). The other olefins **1c**–**5c** were prepared analogously, but in the case of **1c** only a moderate yield (52%) was determined due to a partial decomposition of the substrate. We attempted to convert the carbamates to spiro-γ-amino alcohols by simple hydrolysis, however, **2c** was highly resistant to hydrolytic splitting under the action of methanolic NaOH and even after 6 h of heating under reflux a mixture of products along with remains of **2c** were obtained. On the other hand we observed allylic-type isomerization of the double bond in **2c** in the presence of $MgBr_2·Et_2O$ (10–12 mol-%) in DCM at ambient temperature leading to the sole isomer **2d**. A similar acid-catalyzed isomerization (in a non-spiro system) has been observed previously.[9] Importantly, the same isomerization process did not allow the correct assignment of the structure of carbamate **2c** in a recent publication.[2k] The acidic treatment of the *N*-Boc-spiro-γ-amino alcohol did not produce carbamate **2c** as the authors concluded, but instead its isomer **2d**. This was confirmed by its ^{13}C NMR spectrum which coincides with our spectroscopic data for **2d**. The carbamate **2d**, in contrast to that of **2c**, was easily hydrolyzed to produce diastereomerically pure spiro-β-amino alcohol **2e**.



Scheme 4. Preparation of spiro-β-amino alcohols.

This protocol worked equally well for all the other compounds, although slight differences in reactivity were observed for the hindered carbamates **3c** and **3d**. The isomerization of **3c** only started upon heating the DCM solution and the reaction of **3d** required 12 equiv. of NaOH to complete the hydrolysis. The structure of amino alcohol **3e** was unambiguously established by single-crystal X-ray analysis (Figure 3). The molecules of **3e** formed dimers in the crystal state that were stabilized by O–H···N contacts with an O···N distance equal to 2.797(3) Å.

Table 1. Preparation of spiro-β-amino alcohols; summary of chemical yields and conditions.

n	R	Product, % yield		
		*t*BuOK[a]	$MgBr_2·Et_2O$[b]	NaOH[c]
0	H	52, **1c**	53, **1d**	82, **1e**
1	H	93, **2c**	84, **2d**	84, **2e**
1	CH_3	95, **3c**	99, **3d**	90, **3e**[d]
2	H	87, **5c**	93, **5d**	89, **5e**

[a] 1.2 equiv. of *t*BuOK, –15 °C→r.t., 2 h. [b] 10–12 mol-% $MgBr_2·Et_2O$. [c] 6 equiv. of NaOH, 2 h, reflux. [d] 12 equiv. of NaOH, 4 h reflux.

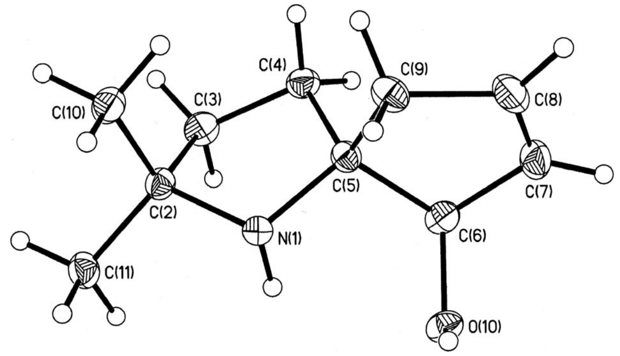
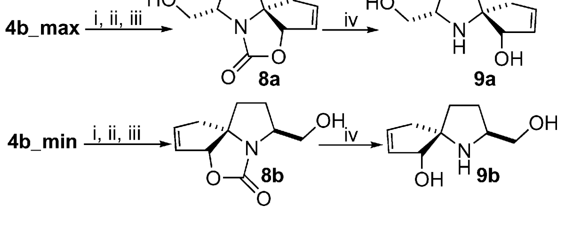
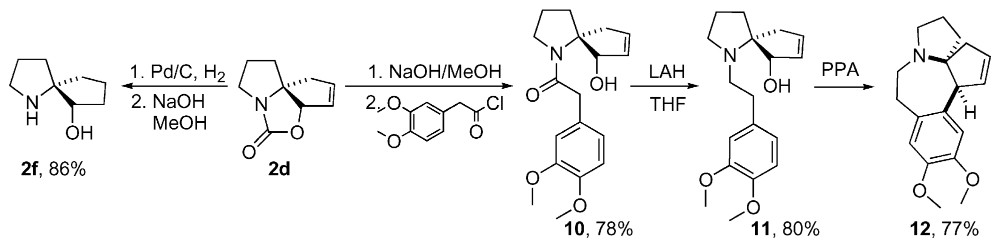


Figure 3. Molecular structure of **3e**.

The two diastereomers of **4b** were transformed to the enantiomerically pure amino alcohols **9a** and **9b** (Scheme 5). Dehydrobromination of the isomers of **4b** proceeded well in the presence of 2 equiv. of *t*BuOK for 3 h and after purification by chromatography **6a** and **6b** were isolated in 94 and 82% yields, respectively. Allylic isomerization gave the pure isomers **7a** and **7b** in 91 and 82% yields after recrystallization. The hydroxy group in **7** was deprotected by using AcOH with gentle heating followed by recrystallization (in the case of **8a**) or by treatment with TBAF at room temperature (in the case of **8b**). Evidently these compounds are suitable for further modification of the hydroxy group giving access to a new pool of chiral products. Hydrolysis of the carbamates **8** produced the target spiro-β-amino diols **9a** and **9b** as only one isomer. Note that some of the spiro-β-amino alcohols (**1e**, **2f**, **9a**, and **9b**) have an unusual ability to induce deuterium–proton exchange between NH, OH,



Scheme 5. Preparation of chiral spiro-β-amino diols. Reagents and conditions: i. 2 equiv. of *t*BuOK, –15 °C→r.t., 3 h, **6a** (94%), **6b** (82%); ii. 10 mol-% $MgBr_2·Et_2O$, **7a** (91%), **7b** (82%), iii. AcOH/THF/H_2O, **8a** (94%); TBAF/THF **8b** (93%); iv. 6 equiv. of NaOH, 2 h, reflux, **9a** (99%), **9b** (93%).



Scheme 6. Preparation of the saturated spiro-β-amino alcohol **2f** and the tetracyclic core of cephalotaxine (**12**).

and $CDCl_3$. As a result, a residual solvent signal of high intensity is observed in their ^1H NMR spectra and a signal corresponding to $CHCl_3$ in the ^{13}C NMR spectra. This is an interesting phenomenon that is currently under study.

Although the alcohols **1e–5e** can be obtained and stored in pure form, it is convenient to prepare them just before their functionalization from stable cyclic carbamates. We performed such a one-pot procedure (hydrolysis and acylation) for carbamate **2d** (Scheme 6). The excess NaOH from the hydrolysis reaction was used as base in the acylation step. Amide **10** was obtained as a crystalline solid and can be purified either by chromatography or crystallization. Reduction of amide **10** by LAH in THF at 0 °C gave rise to amino alcohol **11** which in fact is one of the isomers of Mori's substrate.[2l] We found that **11** was the minor component in a mixture of diastereomeric alcohols.[2l] A comparison of the spectroscopic data allowed us to identify the configuration of the two isomers of Mori's substrate because of the known stereochemistry of the OH group in our isomer. Thus, to ensure the identity of the substrate in the cyclization step a control experiment with **11** was carried out. Heating **11** in the presence of PPA led to the tetracyclic product **12** in 77% yield, which was isolated by chromatography. Its NMR spectrum was identical to that reported by Isono and Mori and hence the formal synthesis of *rac*-cephalotaxine was complete. Also, **2d** was hydrogenated and after hydrolysis the saturated amino alcohol **2f** was obtained in 86% yield for the two steps.

Conclusions

We have elaborated a new method for the synthesis of spiro-β-amino alcohols, which are valuable reagents in natural product synthesis. The method is based on the transformation of Boc-protected azaspiro-olefins to amino alcohols by the halocyclocarmabation–dehydrohalogenation–isomerization–hydrolysis sequence. Most of the steps do not require chromatography and were performed on the mmol scale. The mild conditions used for the allylic-type isomerization may be compatible with other functional groups in similar substrates.

Experimental Section

General: All reactions and manipulations with triallylborane[10] were carried out under dry Ar. Flash chromatography was performed on silica gel (60–230 mesh, Merck). NMR spectra were recorded with Bruker Avance-300, 400, or 600 MHz instruments. Mass spectra were recorded with a Finnigan Polaris Q Ion Trap spectrometer. Melting points were obtained from recrystallized solids and are uncorrected. All solvents and reagents were purified using standard methods. *N*-*tert*-Butoxycarbonyl-1-azaspiro[4.4]non-7-ene (**2a**) and *N*-*tert*-butoxycarbonyl-6-azaspiro[4.5]dec-2-ene (**5a**) were prepared in accordance with the literature procedure.[4a]

***N*-(*tert*-Butoxycarbonyl)-1-azaspiro[3.4]oct-6-ene (1a):** Grubbs' catalyst **I** (0.08 g, 0.097 mmol, 1.3 mol-%) was added in two equal portions, 2 h apart, to a deoxygenated solution of *N*-Boc-2,2-diallylazetidine (1.8 g, 7.6 mmol) in DCM (40 mL) at 40 °C. After the disappearance of the starting material the mixture was concentrated and the residual oil was purified by FC on silica gel in hexane/EtOAc = 6:1 to give 1.52 g (96%) of **1a** as an oil. ^1H NMR (400 MHz, [D$_6$]DMSO, 353 K): δ = 5.62 (s, 2 H), 3.69 (t, J = 7.4 Hz, 2 H), 2.90 (d, J = 15.7 Hz, 2 H), 2.45 (d, J = 15.3 Hz, 2 H), 2.16 (t, J = 7.4 Hz, 2 H), 1.37 (s, 9 H) ppm. Owing to the hindered rotation of the amide group the signals are doubled in the ^{13}C NMR spectrum. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.53, 154.59, 128.81, 128.63, 79.54, 79.33, 73.32, 73.05, 45.66, 45.32, 44.42, 43.87, 33.96, 29.09 ppm. MS (EI, 70 eV): m/z (%) = 209 (3) [M]$^+$, 194 (2), 183 (2), 170 (2), 154 (10), 153 (8), 140 (28), 136 (7), 120 (3), 108 (28), 107 (8), 94 (33), 93 (22), 92 (100), 91 (86), 80 (25), 79 (32), 77 (39), 67 (8), 57 (10), 53 (6), 51 (11), 41 (25), 39 (19). $C_{12}H_{19}NO_2$ (209.2): calcd. C 68.87, H 9.15, N 6.69; found C 68.84, H 9.14, N 6.65.

***N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-1-azaspiro[4.4]non-7-ene (3a):** The procedure followed was similar to that used for the preparation of **1a**. A mixture of *N*-*tert*-butoxycarbonyl-2,2-diallyl-5,5-dimethylpyrrolidine (5.6 g, 20 mmol), Grubbs' catalyst **I** (162 mg, 0.2 mmol, 1.0 mol-%), and CH_2Cl_2 (80 mL) was heated under reflux for 4 h. Flash chromatography was performed on silica gel (hexane/AcOEt = 6:1; R_f = 0.56) to give 4.86 g (97%) of **3a** as a colorless oil. Owing to the hindered rotation of the amide group the signals are doubled in the ^1H NMR spectrum and most of the signals are poorly resolved multiplets in the ^{13}C NMR spectrum. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.68 and 5.61 (both s, total 2 H), 3.13 and 2.95 (both d, J = 15.1 and 15.3 Hz, total 2 H), 2.25–2.13 (m, 2 H), 1.88 and 1.76 (both m, total 4 H), 1.50, 1.43, 1.38 (all s, total 15 H) ppm. MS (EI, 70 eV): m/z (%) = 252 (2) [MH]$^+$, 196 (35), 195 (100), 183 (12), 180 (17), 166 (33), 164 (20), 155 (29), 150 (24), 140 (22), 138 (19), 136 (51), 134 (51), 122 (20), 119 (45), 107 (16), 94 (36), 91 (34), 79 (20), 77 (21), 67 (12), 41 (21), 39 (17). $C_{15}H_{25}NO_2$ (251.4): calcd. C 71.67, H 10.02, N 5.57; found C 71.74, H 10.10, N 5.52.

Procedure for the Reaction of 1a–5a with NBS

(1*R,7*S**,9*R**)-9-Bromo-2-oxa-4-azatricyclo[5.2.1.0$^{4.7}$]decan-3-one (1b):** NBS (2.31 g, 12 mmol) was added to a solution of **1a** (2.09 g, 10 mmol) in 1,2-dichloroethane (30 mL). The mixture was stirred at reflux for 2 h. Then the solvent was removed under reduced pressure. The residue was treated with Et_2O (20 mL) and 10% NaOH (10 mL) and stirred for 15 min. The organic layer was separated, washed with brine (10 mL), dried with K_2CO_3, and the solvents evaporated. The residual oil was purified by flash chromatography in hexane/EtOAc = 1:1 (TLC, hexane/EtOAc = 1:1, R_f = 0.42) to give 1.70 g (73%) of tricyclic bromide **1b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.88 (d, *J* = 3.0 Hz, 1 H), 4.37 (ddd, *J* = 2.0, 4.8, 7.8 Hz, 1 H), 4.09–3.94 (m, 2 H), 3.08 (ddd, *J* = 2.3, 7.8, 14.0 Hz, 1 H), 2.52 (dd, *J* = 6.6, 8.7 Hz, 2 H), 2.37 (dd, *J* = 3.0, 12.5 Hz, 1 H), 2.20 (dd, *J* = 4.8, 14.2 Hz, 1 H), 2.08 (d, *J* = 12.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1; 85.69; 72.56; 49.60; 46.84; 46.38; 34.64; 22.62 ppm. MS (EI, 70 eV): *m/z* (%) = 234/232 (8) $[MH]^+$, 173/171 (2), 153 (8), 152 (79), 124 (15), 109 (11), 108 (77), 106 (17), 96 (8), 95 (6), 94 (4), 93 (6), 82 (9), 81 (26), 80 (100), 79 (48), 77 (36), 67 (7), 65 (10), 53 (44), 51 (13), 39 (12). $C_8H_{10}BrNO_2$ (232.0): calcd. C 41.40, H 4.34, N 6.04, Br 34.43; found C 41.46, H 4.34, N 5.99, Br 34.34.

(1*R,8*S**,10*R**)-10-Bromo-2-oxa-4-azatricyclo[6.2.1.0^{4,8}]undecan-3-one (2b):** The procedure followed was similar to that used for the preparation of **1b**. A mixture of **2a** (2.23 g, 10 mmol) and NBS (2.31 g, 12 mmol) in $CHCl_3$ (30 mL) was stirred under reflux for 1.5 h. After work-up residual oil was crystallized from hexane/Et_2O mixture to give 1.96 g (80%) of the tricyclic bromide **2b** as white crystals, m.p. 123.5–124 °C. R_f = 0.47 (hexane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.43 (d, *J* = 2.3 Hz 1 H), 3.91 (ddd, *J* = 2.0, 4.4, 7.9 Hz, 1 H), 3.19–3.14 (m, 2 H), 2.02 (ddd, *J* = 2.4, 7.9, 14.3 Hz, 1 H), 1.70 (dd, *J* = 2.8, 12.3 Hz, 1 H), 1.39 (dd, *J* = 4.4, 14.3 Hz, 1 H), 1.20–1.01 (m, 5 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 149.66, 83.82, 67.23, 50.49, 48.03, 46.36, 34.81, 32.69, 22.28 ppm. MS (EI, 70 eV): *m/z* (%) = 248/246 (10) $[MH]^+$, 166 (22), 122 (40), 120 (100), 94 (6), 92 (5), 67 (3), 39 (4). $C_9H_{12}BrNO_2$ (246.1): calcd. C 43.92, H 4.91, N 5.69, Br 32.47; found C 43.90, H 4.87, N 5.77, Br 32.54.

(1*S,8*S**,10*S**)-10-Bromo-5,5-dimethyl-4-azatricyclo[6.2.1.0^{4,8}]undecan-3-one (3b):** The procedure followed was similar to that used for the preparation of **1b**. A mixture of **3a** (2.86 g, 11.4 mmol) and NBS (2.63 g, 14.8 mmol) in $CHCl_3$ (6 mL) was stirred under reflux for 30 min. The yield of **3b** after recrystallization was 2.56 g (86.4%), m.p. 102–103 °C (hexane), R_f = 0.62 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (s, 1 H), 4.37–4.34 (m, 1 H), 2.89 (ddd, *J* = 1.8, 7.8, 14.4 Hz, 1 H), 2.50 (dd, *J* = 2.5, 12.6 Hz, 1 H), 2.14 (td, *J* = 10.7, 12.1 Hz, 1 H), 2.05 (dd, *J* = 4.3, 14.8 Hz, 1 H), 1.92 (dm, *J* = 12.3 Hz, 1 H), 1.81–1.73 (m, 3 H), 1.50 (s, 3 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.44, 83.86, 69.57, 63.00, 51.77, 47.59, 38.66, 36.38, 30.60, 28.08, 24.56 ppm. MS (EI, 70 eV): *m/z* (%) = 276/274 (2) $[MH]^+$, 260/258 (3), 232/230 (14), 216/214 (12), 204/202 (4), 194 (66), 159/157 (3), 151/149 (12), 150/148 (100), 134 (23), 117 (7), 107 (10), 106 (14), 105 (14), 94 (25), 93 (20), 91 (20), 81/79 (8), 80 (13), 77 (14), 39 (6). $C_{11}H_{16}BrNO_2$ (274.1): calcd. C 48.19, H 5.88, N 5.11, Br 29.15; found C 48.24, H 5.87, N 5.13, Br 29.01.

(1*R*,5*S*,8*S*,10*R*)-10-Bromo-5-{[*tert*-butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.2.1.0^{4,8}]undecan-3-one (4b_max) and (1*S*,5*S*,8*R*,10*S*)-10-Bromo-5-{[*tert*-butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.2.1.0^{4,8}]undecan-3-one (4b_min): A solution of **4a** (0.90 g, 2.45 mmol) and NBS (0.55 g, 3.12 mmol) in MeCN (5 mL) was stirred for 30 min at 40 °C. TLC [hexane/EtOAc = 1:1; R_f (**4b_max**) = 0.61, R_f (**4b_min**) = 0.46]. Work-up followed by FC gave 0.40 g of **4b_max** and 0.54 g of **4b_min** (total yield 98%).

4b_max: Transparent plates, m.p. 98–99 °C (hexane). $[\alpha]_D^{25}$ = +34.8 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (narrow m, 1 H), 4.38 (ddd, *J* = 1.9, 3.8, 7.9 Hz, 1 H), 3.93–3.90 (m, 2 H), 3.60 (dd, *J* = 4.0, 11.8 Hz, 1 H), 2.94 (ddd, *J* = 2.1, 7.9, 14.8 Hz, 1 H), 2.54 (dd, *J* = 2.6, 12.6 Hz, 1 H), 2.42–2.33 (m, 1 H), 2.10 (dd, *J* = 4.0, 14.8 Hz, 1 H), 1.98–1.87 (m, 4 H), 0.87 (s, 9 H), 0.03 and 0.02 (both s, total 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.24, 84.27, 68.75, 62.26, 59.43, 51.19, 47.46, 34.89, 32.35, 26.22, 25.92 (3 CH_3), 18.19, –5.36, –5.56 ppm. $C_{16}H_{28}BrNO_3Si$ (390.4): calcd. C 49.23, H 7.23, Si 7.19; found C 49.25, H 7.21, Si 7.20.

4b_min: Transparent needles, m.p. 78–79 °C (hexane). $[\alpha]_D^{25}$ = –87.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.75 (d, *J* = 2.3 Hz, 1 H), 4.30 (ddd, *J* = 1.8, 4.3, 8.0 Hz, 1 H), 4.01 (dd, *J* = 3.9, 10.3 Hz, 1 H), 3.94–3.90 (m, 1 H), 3.54 (dd, *J* = 2.3, 10.3 Hz, 1 H), 3.09 (ddd, *J* = 2.1, 7.8, 14.4 Hz, 1 H), 2.41 (dd, *J* = 2.7, 12.6 Hz, 1 H), 2.09–1.87 (m, 5 H), 1.80 (d, *J* = 12.6 Hz, 1 H), 0.86 (s, 9 H), 0.03 and 0.02 (both s, total 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.41, 84.19, 69.01, 62.00, 60.64, 50.67, 47.54, 35.60, 31.82, 25.93 (3 CH_3), 25.18, 18.32, –5.29, –5.55 ppm. MS (EI, 70 eV): *m/z* (%) = 392/390 (0.8) $[MH]^+$, 334/332 (40), 290/288 (18), 209 (13), 208 (63), 134 (10), 118 (10), 117 (21), 116 (100), 75 (11). $C_{16}H_{28}BrNO_3Si$ (390.4): calcd. C 49.23, H 7.23, Si 7.19; found C 49.21, H 7.19, Si 7.26.

(1*R,9*S**,11*R**)-9-Bromo-2-oxa-4-azatricyclo[7.2.1.0^{4,9}]dodecan-3-one (5b):** The procedure followed was similar to that used for the preparation of **1b**. A mixture of **5a** (1.0 g, 4.3 mmol) and NBS (0.9 g, 5 mmol) in DCM (15 mL) was stirred at 25 °C for 2 h. Work up followed by FC gave 0.9 g (80.5%) of the tricyclic bromide **5b** as white crystals, m.p. 124–124.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.73 (m, 1 H), 4.46 (ddd, *J* = 2.0, 4.3, 8.0 Hz, 1 H), 4.11 (dm, *J* = 13.5 Hz 1 H), 3.21 (ddd, *J* = 2.1, 7.8, 15.1 Hz, 1 H), 2.8 (dt, *J* = 3.4, 13.5 Hz, 1 H), 2.39 (dd, *J* = 4.4, 14.3 Hz, 1 H), 2.14 (d, *J* = 13.0 Hz, 1 H), 1.98 (dd, *J* = 4.3, 15.1 Hz, 1 H), 1.84–1.77 (m, 4 H), 1.54–1.31 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.15, 82.89, 63.32, 47.83, 47.57, 41.42, 38.82, 33.48, 24.57, 20.73 ppm. MS (EI, 70 eV): *m/z* (%) = 262/260 (0.5) $[MH]^+$, 218/216 (3), 180 (37), 137/135 (11), 136 (60), 134 (100), 108 (6), 94 (9), 93 (9), 91 (5), 55 (6), 39 (3). $C_{10}H_{14}BrNO_2$ (260.1): calcd. C 46.17, H 5.42, N 5.38, Br 30.72; found C 46.24, H 5.32, N 5.42, Br 30.68.

Procedure for the Reaction of 1b–5b with *t*BuOK

(1*R,7*S**)-2-Oxa-4-azatricyclo[5.2.1.0^{4,7}]dec-8-en-3-one (1c):** A solution of bromide **1b** (1.1 g, 4.7 mmol) in THF (3 mL) was added to a solution of *t*BuOK (1.06 g, 9.4 mmol) in THF (10 mL) at –15 °C under Ar with stirring. The mixture was warmed to room temperature and stirring was continued for 1.5 h [TLC, hexane/EtOAc = 1:1; R_f = 0.27]. The solvent was removed under reduced pressure and water (3 mL) and DCM (15 mL) were added to the residue and shaken. The organic layer was separated and the aqueous one extracted with DCM (10 mL). The combined extracts were dried with Na_2SO_4 and the solvents evaporated. The residue was purified by FC in hexane/EtOAc = 3:2 to give 0.37 g (52%) of **1c** as a solid, m.p. 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.66 (d, *J* = 5.6 Hz, 1 H), 6.19 (dd, *J* = 2.5, 5.5 Hz, 1 H), 5.16 (s, 1 H), 4.05 (d, *J* = 8.4 Hz, 1 H), 4.04 (d, *J* = 8.3 Hz, 1 H), 2.78 (dt, *J* = 8.6, 12.1 Hz, 1 H), 2.49 (dt, *J* = 6.8, 12.2 Hz, 1 H), 2.17 (dd, *J* = 2.4, 10.8 Hz, 1 H), 2.11 (d, *J* = 10.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.97, 145.01, 132.23, 81.89, 73.43, 47.95, 44.56, 24.06 ppm. MS (EI, 70 eV): *m/z* (%) = 151 (17) $[M]^+$; 136 (4), 123 (5), 122 (14), 120 (11), 108 (10), 107 (29), 106 (100), 95 (24), 94 (34), 92 (13), 81 (7), 80 (22), 79 (59), 78 (41), 77 (62), 67 (14), 65 (17), 53 (10), 52 (18), 51 (25), 50 (19), 39 (17). $C_8H_9NO_2$ (151.2): calcd. C 63.56, H 6.00, N 9.27; found C 63.53, H 6.20, N 9.19.

(1*R,8*S**)-2-Oxa-4-azatricyclo[6.2.1.0^{4,8}]undec-9-en-3-one (2c):** The procedure followed was similar to that used for the preparation of **1c**. Bromide **2b** (1.23 g, 5.0 mmol) produced 0.77 g (93%) of olefin **2c** as a solid, m.p. 63–64 °C (hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.32 (d, J = 5.5 Hz, 1 H), 6.19 (unresolved dd, J = 5.5 Hz, 1 H), 5.13 (s, 1 H), 3.62–3.56 (m, 1 H), 3.44–3.56 (m, 1 H), 2.26–2.21 (m, 1 H), 2.14 (d, J = 11.4 Hz, 1 H), 2.10–1.90 (m, 3 H), 1.85 (d, J = 10.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 151.44, 142.85, 131.00, 80.73, 69.12, 45.25, 43.69, 31.65, 22.98 ppm. MS (EI, 70 eV): *m/z* (%) = 165 (18) [M]$^+$; 136 (21), 121 (16), 120 (100), 118 (8), 109 (6), 108 (11), 93 (12), 92 (24), 80 (8), 77 (5), 66 (9), 65 (12), 39 (7). C$_9$H$_{11}$NO$_2$ (165.2): calcd. C 65.44, H 6.71, N 8.48; found C 65.41, H 6.71, N 8.37.

(1*S,8*S**)-5,5-Dimethyl-4-azatricyclo[6.2.1.0^{4,8}]undec-9-en-3-one (3c):** The procedure followed was similar to that used for the preparation of **1c**. Bromide **3b** (2.34 g, 8.5 mmol) produced 1.64 g (100%) of olefin **3c** as a solid. The yield after recrystallization was 1.56 g (95%), m.p. 100–100.5 °C (hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.28 (d, J = 5.2 Hz, 1 H), 6.04 (m, 1 H), 5.01 (s, 1 H), 2.08 (d, J = 10.7 Hz, 1 H), 2.04–2.02 (m, 2 H), 1.87–1.85 (m, 2 H), 1.73 (d, J = 10.9 Hz, 1 H), 1.46 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 150.14, 142.31, 130.47, 80.19, 70.78, 61.54, 44.65, 39.22, 28.76, 28.13, 24.90 ppm. MS (EI, 70 eV): *m/z* (%) = 193 (4) [M]$^+$, 178 (39), 164 (6), 149 (16), 148 (46), 135 (11), 134 (100), 133 (10), 132 (70), 117 (20), 107 (9), 106 (25), 94 (9), 93 (22), 91 (30), 80 (8), 79 (7), 77 (17), 65 (15), 39 (8). C$_{11}$H$_{15}$NO$_2$ (193.2): calcd. C 68.37, H 7.82, N 7.25; found C 68.42, H 7.79, N 7.27.

(1*R*,5*S*,8*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.2.1.0^{4,8}]undec-9-en-3-one (6a): The procedure followed was similar to that used for the preparation of **1c**. Bromide **4b_max** (1.4 g, 3.6 mmol) produced 1.03 g (94%) of olefin **6a** as solid, transparent crystals, m.p. 58–59 °C (hexane). $[\alpha]_D^{25}$ = –17.0 (c = 1, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.23 (d, J = 5.2 Hz, 1 H), 6.08 (m, 1 H), 5.04 (s, 1 H), 3.88 (br. s, 1 H), 3.80 (dd, J = 4.8, 10.0 Hz, 1 H), 3.60 (d, J = 10.0 Hz, 1 H), 2.21 (m, 1 H), 2.06–1.97 (m, 4 H), 1.81 (d, J = 10.7 Hz, 1 H), 0.81 (s, 9 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 150.93, 142.44, 131.01, 80.82, 70.17, 62.85, 58.22, 43.37, 30.24, 26.40, 25.91, 18.17, –5.38, –5.56 ppm. MS (EI, 70 eV): *m/z* (%) = 309(0.1) [M]$^+$, 264 (3), 252 (11), 250 (7), 209 (20), 208 (100), 180 (12), 120 (5), 118 (5), 75 (4). C$_{16}$H$_{27}$NO$_3$Si (309.5): calcd. C 62.10, H 8.79, Si 9.08; found C 62.03, H 8.85, Si 9.09.

(1*S*,5*S*,8*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.2.1.0^{4,8}]undec-9-en-3-one (6b): Bromide **4b_min** (1.98 g, 5.07 mmol) produced 1.28 g (82%) of olefin **6b** as a solid, m.p. 33–34 °C. $[\alpha]_D^{25}$ = –88.7 (c = 1, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.22 (d, J = 5.2 Hz, 1 H), 6.08 (dd, J = 2.0, 5.2 Hz, 1 H), 4.98 (s, 1 H), 3.88 (m, 1 H), 3.82 (dd, J = 4.8, 10.0 Hz, 1 H), 3.58 (dd, J = 2.0, 9.9 Hz, 1 H), 2.25–2.13 (m, 1 H), 2.08–1.90 (m, 4 H), 1.75 (d, J = 10.7 Hz, 1 H), 0.79 (s, 9 H), –0.04 and –0.06 (both s, 6 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 151.16, 144.29, 130.20, 80.64, 70.01, 62.58, 59.18, 44.05, 30.16, 25.92, 25.79, 18.28, –5.30, –5.56 ppm. C$_{16}$H$_{27}$NO$_3$Si (309.5): calcd. C 62.10, H 8.79, Si 9.08; found C 62.14, H 8.76, Si 9.11.

(1*R,9*S**)-2-Oxa-4-azatricyclo[7.2.1.0^{4,9}]dodec-10-en-3-one (5c):** The procedure followed was similar to that used for the preparation of **1c**. Bromide **5b** (0.35 g, 1.35 mmol) produced 0.22 g (87%) of olefin **5c** as a solid, m.p. 83.5–84.5 °C. ^{1}H NMR (600 MHz, CDCl$_3$): δ = 6.60 (d, J = 6.0 Hz, 1 H), 6.21 (dd, J = 2.3, 5.5 Hz, 1 H), 4.92 (s, 1 H), 4.00 (dt, J = 1.8, 13.3 Hz, 1 H), 2.72 (td, J = 3.2, 13.3 Hz, 1 H), 2.03 (d, J = 11.4 Hz, 1 H), 1.86 (dd, J = 2.3, 11.5 Hz, 1 H), 1.83–1.71 (m, 4 H), 1.51–1.43 (m, 2 H) ppm. ^{13}C NMR (150 MHz, CDCl$_3$): δ = 153.73, 141.78, 132.68, 79.14, 64.52, 46.40, 42.61, 31.20, 24.72, 21.00 ppm. MS (EI, 70 eV): *m/z* (%) = 179 (11) [M]$^+$, 160 (8), 158 (8), 150 (12), 138 (9), 136 (9), 135 (27), 134 (100), 122 (17), 120 (15), 119 (10), 118 (18), 106 (17), 94 (10), 93 (21), 92 (17), 91 (10), 80 (9), 79 (11), 77 (8), 65 (7), 39 (6). C$_{10}$H$_{13}$NO$_2$ (179.2): calcd. C 67.02, H 7.31, N 7.82; found C 66.98, H 7.34, N 7.79.

Procedure for the Isomerization of 1c–5c with MgBr$_2$·Et$_2$O

(1*R,7*S**)-2-Oxa-4-azatricyclo[5.3.0$^{1.7}$.0$^{4.7}$]dec-9-en-3-one (1d):** MgBr$_2$·Et$_2$O (80 mg, 0.3 mmol, 12 mol-%) was added to a solution of **1c** (0.35 g, 2.4 mmol) in DCM (5 mL). The mixture was stirred at room temperature for 1 h (TLC, hexane/EtOAc = 3:2; R_f = 0.42). After the rearrangement was complete water (0.2 mL) was added to separate the magnesium salt. The solution obtained was passed through a layer of Super-cel Hyflo, which after evaporation and FC purification gave 0.18 g (53%) of **1d** as a solid, m.p. 69–70 °C (hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.05–6.03 (m, 1 H), 5.82 (ddd, J = 2.1, 4.1, 5.9 Hz, 1 H), 5.35 (s, 1 H), 4.22 (dt, J = 9.3, 7.5 Hz, 1 H), 3.82 (td, J = 3.9, 9.3 Hz, 1 H), 3.19 (dt, J = 9.6, 11.9 Hz, 1 H), 3.11 (ddd, J = 1.8, 3.9, 18.1 Hz, 1 H), 2.69 (dm, J = 18.0 Hz, 1 H), 2.50 (ddd, J = 3.9, 7.6, 11.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.30, 135.46, 128.37, 90.43, 74.33, 51.49, 43.41, 31.40 ppm. MS (EI, 70 eV): *m/z* (%) = 152 (10) [MH]$^+$, 151 (1) [M]$^+$, 150 (4), 138 (4), 123 (10), 122 (21), 108 (7), 107 (16), 106 (89), 105 (6), 104 (9), 96 (5), 95 (68), 94 (26), 92 (61), 81 (12), 80 (24), 79 (94), 78 (61), 77 (100), 68 (14), 67 (43), 65 (33), 53 (13), 52 (40), 51 (54), 50 (28), 41 (12), 39 (28). C$_8$H$_9$NO$_2$ (151.2): calcd. C 63.56, H 6.00, N 9.27; found C 63.75, H 6.07, N 9.10.

(1*R,8*S**)-2-Oxa-4-azatricyclo[6.3.0$^{1.8}$.0$^{4.8}$]undec-10-en-3-one (2d):** The procedure followed was similar to that used for the preparation of **1d**. Olefin **2c** (0.25 g, 1.5 mmol) produced 0.21 g (84%) of **2d** as a solid, m.p. 58–59 °C (hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.06–6.04 (m, 1 H), 5.87 (ddd, J = 1.8, 4.1, 5.9 Hz, 1 H), 5.22 (s, 1 H), 3.61 (ddd, J = 6.8, 8.0, 11.6 Hz, 1 H), 3.19 (ddd, J = 4.3, 8.4, 11.6 Hz, 1 H), 2.68 (ddd, J = 2.1, 4.3, 17.3 Hz, 1 H), 2.35 (dm, J = 17.3 Hz, 1 H), 2.21–2.08 (m, 1 H), 2.07–1.83 (m, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.56, 135.55, 128.88, 87.88, 73.96, 44.75, 44.28, 34.74, 25.78 ppm. MS (EI, 70 eV): *m/z* (%) = 165 (4) [M]$^+$, 148 (4), 136 (11), 121 (23), 120 (100), 118 (6), 106 (4), 93 (11), 92 (9), 80 (5), 66 (6), 65 (7), 39 (5). C$_9$H$_{11}$NO$_2$ (165.2): calcd. C 65.44, H 6.71, N 8.48; found C 65.59, H 6.74, N 8.54.

(1*R,8*S**)-5,5-Dimethyl-2-oxa-4-azatricyclo[6.3.0$^{1.8}$.0$^{4.8}$]undec-10-en-3-one (3d):** The procedure followed was similar to that used for the preparation of **1d**. Olefin **3c** (1.454 g, 5.53 mmol) produced 1.451 g (99%) of **3d** as a solid, m.p. 85.5–86.5 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 6.09–6.07 (m, 1 H), 5.89–5.85 (m, 1 H), 5.06 (s, 1 H), 2.81 (d, J = 17.6 Hz, 1 H), 2.47 (d, J = 17.6 Hz, 1 H), 2.10–1.98 (m, 3 H), 1.89–1.81 (m, 1 H), 1.48 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 156.78, 136.75, 128.40, 87.10, 75.09, 60.46, 47.79, 43.10, 35.97, 29.78, 24.41 ppm. MS (EI, 70 eV): *m/z* (%) = 193 (17) [M]$^+$, 164 (11), 150 (11), 149 (60), 148 (99), 134 (100), 132 (53), 122 (10), 121 (13), 120 (12), 117 (20), 106 (44), 93 (45), 91 (40), 80 (16), 77 (19), 65 (20), 39 (11). C$_{11}$H$_{15}$NO$_2$ (193.2): calcd. C 68.37, H 7.82, N 7.25; found C 68.25, H 7.78, N 7.15.

(1*R*,5*S*,8*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.3.0$^{1.8}$0$^{4.8}$]undec-10-en-3-one (7a): The procedure followed was similar to that used for the preparation of **1d**. Olefin **6a** (0.96 g, 3.1 mmol) produced 0.87 g (91%) of **7a** as a solid, m.p. 56–57 °C. $[\alpha]_D^{25}$ = –55.3 (c = 1, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 6.02 (m, 1 H), 5.85 (m, 1 H), 5.19 (s, 1 H), 3.86 (m, 1 H), 3.70 (m, 2 H), 2.95 (d, J = 17.6 Hz, 1 H), 2.32 (d, J = 17.6 Hz, 1 H), 2.23–2.02 (m, 2 H), 1.95–1.84 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 161.09, 135.64, 128.63, 87.99, 74.17, 64.67, 60.61, 45.03, 36.18, 28.75, 25.92, 18.39, –5.36,

–5.48 ppm. $C_{16}H_{27}NO_3Si$ (309.5): calcd. C 62.10, H 8.79, N 4.53, Si 9.08; found C 62.08, H 8.74, N 4.56, Si 9.12.

(1*S*,5*S*,8*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxymethyl}-2-oxa-4-azatricyclo[6.3.0$^{1.8}$0$^{4.8}$]undec-10-en-3-one (7b): The procedure followed was similar to that used for the preparation of **1d**. Olefin **6b** (1.10 g, 3.6 mmol) produced 0.90 g (82%) of **7b** as a solid, m.p. 43.5–44.5 °C. $[\alpha]_{\mathrm{D}}^{25}$ = +30.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.05 (dt, *J* = 2.4, 5.9 Hz, 1 H), 5.83 (ddd, *J* = 2.2, 4.5, 5.9 Hz, 1 H), 5.08 (t, *J* = 2.0 Hz, 1 H), 4.38 (dd, *J* = 3.8, 10.1 Hz, 1 H), 3.70 (dd, *J* = 2.2, 10.2 Hz, 1 H), 3.64 (dddd, *J* = 1.6, 2.2, 3.8, 8.5 Hz, 1 H), 2.73 (ddd, *J* = 2.3, 4.5, 17.6 Hz, 1 H), 2.38 (dt, *J* = 2.3, 17.6 Hz, 1 H), 2.28–2.09 (m, 3 H), 1.71–1.67 (m, 1 H), 0.86 (s, 9 H), 0.04 and 0.03 (both s, total 6 H) ppm. A splitting of several signals was observed in the ^{13}C NMR spectrum and are shown in parentheses. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.94, 136.59, 128.55, 87.35, 75.14, 60.90, (57.21, 57.13), 47.00, 35.55, 31.97, (26.09, 25.82, 25.79, 25.52), 18.15, (–5.58, –5.62), (–5.71, –5.74) ppm. MS (EI, 70 eV): *m*/*z* (%) = 309(0.1) [M]$^+$, 252 (16), 250 (6), 209 (17), 208 (100), 206 (5), 180 (12), 134 (6), 132 (5), 75 (4). $C_{16}H_{27}NO_3Si$ (309.5): calcd. C 62.10, H 8.79, N 4.53, Si 9.08; found C 62.19, H 8.77, N 4.54, Si 9.01.

(1*R,9*S**)-2-Oxa-4-azatricyclo[7.3.0.$^{1.9}$0$^{4.9}$]dodec-11-en-3-one (5d):** The procedure followed was similar to that used for the preparation of **1d**. Olefin **5c** (0.21 g, 1.2 mmol) produced 0.19 g (93%) of **5d** as a solid, m.p. 88.5–89.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.07–6.05 (m, 1 H), 5.84 (ddd, *J* = 2.04, 4.1, 5.7 Hz, 1 H), 5.00 (s, 1 H), 3.89 (dd, *J* = 4.35, 13.5 Hz, 1 H), 2.91 (td, *J* = 3.4, 13.5 Hz, 1 H), 2.80 (ddd, *J* = 2.1, 4.3, 17.6 Hz, 1 H), 2.40 (dd, *J* = 2.0, 17.6 Hz, 1 H), 1.94–1.91 (m, 1 H), 1.81–1.44 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.73, 135.54, 128.31, 88.40, 65.35, 41.84, 39.35, 34.94, 24.90, 21.07 ppm. MS (EI, 70 eV): *m*/*z* (%) = 179 (23) [M]$^+$, 135 (28), 134 (100), 120 (16), 107 (11), 106 (17), 93 (9), 92 (5), 80 (5), 79 (7), 77 (5), 65 (4), 39 (4). $C_{10}H_{13}NO_2$ (179.2): calcd. C 67.02, H 7.31, N 7.82; found C 66.85, H 7.38, N 7.77.

Procedure for the Alkaline Hydrolysis of 1d–5d with NaOH

(4*R,5*S**)-1-Azaspiro[3.4]oct-6-en-5-ol (1e):** Solid NaOH (0.26 g, 6.5 mmol) was added to a solution of carbamate **1d** (0.20 g, 1.3 mmol) in a mixture of MeOH (2.0 mL) and water (0.5 mL). The mixture was heated at reflux with stirring for 2.5 h, until the disappearance of a spot of **1d** on a TLC plate (hexane/EtOAc = 1:1). Then the MeOH was evaporated under reduced pressure, DCM (30 mL) was added, and the resulting suspension was dried with K_2CO_3, filtered, and concentrated in vacuo to afford 0.13 g (82%) of pure amino alcohol **1e** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 (s, 1 H), 5.61 (s, 1 H), 4.16 (s, 1 H), 3.39 (dd, *J* = 8.0, 15.7 Hz, 1 H), 3.21 (dd, *J* = 8.0, 13.4 Hz, 1 H) 2.55 (d, *J* = 17.0 Hz, 1 H), 2.43 (d, *J* = 16.8 Hz, 1 H), 2.27–2.20 (m, 1 H), 2.15–2.09 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.32, 130.89, 79.23, 69.90, 45.03, 41.20, 29.92 ppm. MS (EI, 70 eV): the product was too volatile to record a mass spectrum. $C_7H_{11}NO$ (125.2): calcd. C 67.17, H 8.86, N 11.19; found C 67.32, H 9.06, N 11.13.

(5*R,6*S**)-1-Azaspiro[4.4]non-7-en-6-ol (2e):** The procedure followed was similar to that used for the preparation of **1e**. Carbamate **2d** (0.33 g, 2.0 mmol) produced 0.24 g (84%) of amino alcohol **2e** as a solid, m.p. 34–35 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (dtd, *J* = 0.7, 2.3, 5.9 Hz, 1 H), 5.79 (ddd, *J* = 2.0, 3.9, 5.9 Hz, 1 H), 4.01 (s, 1 H), 3.37 (br. s, 2 H, NH and OH), 3.03 (dt, *J* = 7.1, 10.0 Hz 1 H) 2.60 (dt, *J* = 6.2, 10.0 Hz 1 H), 2.41 (s, 2 H), 1.88–1.70 (m, 4 H) ppm. A splitting of one signal was observed in the ^{13}C NMR spectrum and is shown in parentheses. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.72, 132.32, (79.87, 79.33, 78.88), 69.84, 46.12, 45.39, 37.78, 25.89 ppm. MS (EI, 70 eV): *m*/*z* (%) = 139 (45) [M]$^+$, 138 (59), 123 (31), 122 (58), 120 (87), 117 (61), 110 (51), 109 (32), 97 (43), 95 (45), 91 (37), 83 (100), 82 (95), 80 (42), 79 (47), 77 (37), 67 (51), 57 (32), 55 (26), 41 (34), 39 (25). $C_8H_{13}NO$ (139.2): calcd. C 69.03, H 9.41, N 10.06; found C 68.99, H 9.46, N 10.01.

(5*R,6*S**)-1-Azaspiro[4.4]nonan-6-ol (2f):** The procedure followed was similar to that used for the preparation of **1e**. A carbamate (0.30 g, 1.8 mmol) obtained after hydrogenation of **2d** produced 0.233 g (92%) of amino alcohol **2f** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 (dd, *J* = 2.2, 4.2 Hz, 1 H), 2.92 (dt, *J* = 5.1, 8.0 Hz, 1 H), 2.71 (dt, *J* = 4.9, 8.0 Hz, 1 H), 1.80–1.42 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.53, 71.76, 46.10, 36.78 2C, 32.36, 26.49, 20.90 ppm. MS (EI, 70 eV): *m*/*z* (%) = 141 (12) [M]$^+$, 125 (10), 123 (34), 119 (41), 112 (31), 110 (31), 97 (45), 95 (40), 91 (31), 83 (100), 82 (98), 80 (50), 79 (37), 76 (22), 57 (29), 55 (16), 41 (24), 39 (32). $C_8H_{15}NO$ (141.2): calcd. C 68.04, H 10.71, N 9.92; found C 67.93, H 10.75, N 9.91.

(5*R,6*S**)-2,2-Dimethyl-1-azaspiro[4.4]non-7-en-6-ol (3e):** The procedure followed was similar to that used for the preparation of **1e**. Carbamate **3d** (1.253 g, 6.5 mmol) produced 0.978 g (90%) of **3e** as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.81 (dtd, *J* = 0.5, 2.1, 6.1 Hz, 1 H), 5.77 (ddd, *J* = 2.1, 3.7, 5.9 Hz, 1 H), 3.93 (s, 1 H), 3.12 (br. s, 2 H), 2.45 (dtd, *J* = 0.7, 2.3, 16.7 Hz, 1 H), 2.39 (ddd, *J* = 1.8, 3.7, 16.7 Hz, 1 H), 1.99–1.84 (m, 2 H), 1.72–1.58 (m, 2 H), 1.22 (s, 3 H), 1.48 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 133.89, 131.97, 79.28, 70.56, 59.14, 46.75, 39.59, 37.69, 30.34, 30.19 ppm. MS (EI, 70 eV): *m*/*z* (%) = 167 (17) [M]$^+$, 166 (15), 150 (30), 149 (48), 148 (85), 134 (73), 132 (54), 117 (22), 111 (45), 106 (45), 96 (100), 94 (26), 93 (47), 91 (44), 82 (16), 81 (16), 80 (22), 79 (22), 77 (27), 65 (22), 39 (14). $C_{10}H_{17}NO$ (167.2): calcd. C 71.81, H 10.25, N 8.37; found C 71.89, H 10.26, N 8.21.

(2*S*,5*S*,6*R*)-2-(Hydroxymethyl)-1-azaspiro[4.4]non-7-en-6-ol (9a): The procedure followed was similar to that used for the preparation of **1e**. Carbamate **8a** (0.37 g, 1.9 mmol) produced 0.318 g (99%) of amino alcohol **9a** as an oil. $[\alpha]_{\mathrm{D}}^{25}$ = +82.7 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.29 (m, 1 H), 5.81 (s, 1 H), 4.03 (s, 1 H), 3.60 (dd, *J* = 3.0, 11.0 Hz, 1 H), 3.41 (dd, *J* = 7.5, 11.0 Hz, 1 H), 3.30–3.27 (m, 1 H), 2.50 (d, *J* = 16.7 Hz, 1 H), 2.33 (d, *J* = 16.7 Hz, 1 H), 1.91–1.68 (m, 3 H), 1.62–1.53 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.01, 132.56, 79.15, 70.05, 65.21, 59.33, 45.14, 37.45, 27.60 ppm. MS (EI, 70 eV): *m*/*z* (%) = 169 (8) [M]$^+$, 168 (5), 152 (21), 150 (17), 138 (58), 121 (11), 120 (75), 118 (59), 113 (34), 106 (17), 103 (25), 95 (12), 94 (24), 93 (16), 91 (34), 82 (100), 80 (23), 79 (14), 77 (29), 67 (20), 39 (11). $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.69, H 9.06, N 8.16.

(2*R*,5*S*,6*S*)-2-(Hydroxymethyl)-1-azaspiro[4.4]non-7-en-6-ol (9b): The procedure followed was similar to that used for the preparation of **1e**. Carbamate **8b** (0.137 g, 0.7 mmol) produced 0.11 g (93%) of amino alcohol **9b** as an oil. $[\alpha]_{\mathrm{D}}^{25}$ = –48.9 (*c* = 0.5, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.82 (s, 1 H), 5.77 (s, 1 H), 3.99 (s, 1 H), 3.55 (br. s, 1 H), 3.38–3.36 (br. m, 2 H), 2.45 (d, *J* = 16.5 Hz, 1 H), 2.32 (d, *J* = 16.5 Hz, 1 H), 1.83 (br. m, 2 H), 1.72–1.70 (m, 1 H), 1.54 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 133.48, 132.62, 79.40, 70.15, 65.80, 59.18, 45.14, 37.37, 27.34 ppm. $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.70, H 9.10, N 8.12.

(1*S,5*R**)-6-Azaspiro[4.5]dec-2-en-1-ol (5e):** The procedure followed was similar to that used for the preparation of **1e**. Carbamate **5d** (0.18 g, 1.0 mmol) produced 0.13 g (89%) of amino alcohol **5e** as a solid, m.p. 87–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.82 (m, 1 H), 5.77–5.75 (m, 1 H), 4.24 (br. s, 2 H, OH and NH), 4.11 (s, 1 H), 2.89 (d, *J* = 11.4 Hz 1 H), 2.66 (t, *J* = 10.7 Hz, 1 H), 2.31 (t, J = 17.8 Hz, 2 H), 1.64–1.42 (m, 6 H) ppm. A splitting of one signal was observed in the ^{13}C NMR spectrum and is shown in parentheses. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.51, 132.08, (81.51, 81.14, 81.05, 80.67), 60.98, 42.56, 40.70, 35.03, 25.64, 21.66 ppm. MS (EI, 70 eV): m/z (%) = 153(7) [M]$^+$, 152 (7), 137 (6), 136 (48), 134 (31), 132 (5), 125 (5), 124 (14), 122 (12), 120 (6), 118 (5), 117 (6), 110 (14), 108 (13), 106 (14), 97 (100), 96 (84), 94 (15), 93 (11), 91 (13), 82 (18), 80 (14), 79 (10), 77 (11), 68 (9), 67 (9), 54 (11), 41 (7), 39 (8). $C_9H_{15}NO$ (153.2): calcd. C 70.55, H 9.87, N 9.14; found C 70.71, H 10.15, N 8.98.

Preparation of the Tetracycle 12 – Precursor for Cephalotaxine Synthesis

(5*R**,6*S****)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-1-azaspiro[4.4]non-7-en-6-ol (11):** A solution of amide **10** (0.40 g, 1.26 mmol) in THF (8 mL) was added dropwise to a solution of LAH (0.38 g, 1.0 mmol) in THF (6 mL) at 0–5 °C. The mixture was stirred for 1.5 h at 25 °C and then one more portion of LAH (0.38 g, 1.0 mmol) was added and the mixture was stirred for a further 0.5 h. TLC control (hexane/EtOAc = 1:1, R_f = 0.15). After the reaction was complete, 10% NaOH (2 mL) was added, the precipitated salt was filtered, washed with THF (4 × 5 mL), and the filtrate evaporated under reduced pressure. The residual oil was subjected to FC in hexane/EtOAc = 1:1 to give 0.31 g (80%) of amine **11** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$):[2] δ = 6.80–6.70 (m, 3 H), 5.78 (t, J = 7.68 Hz, 2 H), 4.19 (s, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.37–3.32 (m, 1 H), 2.96 (ddd, J = 7.4, 9.6, 11.4 Hz, 1 H), 2.79 (ddd, J = 4.4, 9.0, 13.4 Hz, 1 H), 2.70 (d, J = 16.4 Hz 1 H), 2.74–2.66 (m, 1 H), 2.59–2.49 (m, 2 H), 2.12 (d, J = 17.6 Hz, 1 H), 2.09–2.03 (m, 1 H), 1.89–1.73 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.81, 147.42, 134.37, 132.32, 131.17, 120.60, 112.05, 111.17, 80.63, 72.30 (2 C), 55.86, 52.91, 52.74, 39.28, 38.23, 35.70, 23.16 ppm. $C_{18}H_{25}NO_3$ (303.4): calcd. C 71.26, H 8.31, N 4.62; found C 71.31, H 8.20, N 4.57.

(3a*S**,13b*S****)-3,5,6,8,9,13b-Hexahydro-11,12-dimethoxy-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepine (12):**[2] Amine **11** (0.318 g, 1.05 mmol) was mixed with PPA (9 g) and stirred at 60 °C for 30 h. The reaction mixture was treated with satd. $NaHCO_3$ (15 mL) and then solid NaOH was added to adjust the pH to 10. The mixture was extracted with DCM (20 mL × 3) and then the extracts were dried with K_2CO_3, filtered, and the solvent evaporated. The residual oil was purified by chromatography with hexane/EtOAc/Et_3N = 70:50:1 as eluent to afford 0.23 g (77%) of tetracycle **12** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.62 (s, 1 H), 5.80–5.77 (m, 1 H), 5.55–5.52 (m, 1 H), 3.89 (m, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.21 (ddd, J = 7.6, 12.6, 13.5 Hz, 1 H), 3.08 (ddd, J = 4.8, 8.9, 9.3 Hz, 1 H), 2.94 (ddd, J = 6.8, 11.6, 12.1 Hz, 1 H), 2.76 (ddd, J = 2.5, 4.8, 17.6 Hz, 1 H), 2.56 (dd, J = 7.5, 11.4 Hz, 1 H), 2.43–2.32 (m, 2 H), 2.04–1.95 (m, 3 H), 1.80–1.67 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.43, 147.07, 132.43, 130.98, 130.79, 128.53, 113.99, 112.95, 68.08, 62.24, 56.02, 55.93, 53.65, 49.07, 43.31, 34.71, 30.37, 19.88 ppm.

X-ray Crystal Structure Determination for 2b: $C_9H_{12}BrNO_2$, M = 246.11, orthorhombic, space group $Pna2_1$, T = 293 K, a = 9.0704(11), b = 13.3202(16), c = 7.9647(10) Å, V = 962.3(2) Å^3, Z = 4, $F(000)$ = 496, $d_{\text{calcd.}}$ = 1.699 g/cm^3, μ = 4.238 mm^{-1}. Data were collected with a Bruker three-circle diffractometer equipped with a SMART 1K CCD detector [λ(Mo-K_α) radiation, graphite monochromator, ϕ and ω scan mode, $\theta_{\max}$ = 26°] and corrected for Lorentzian and polarization effects and for absorption. The structure was determined by direct methods and refined by a full-matrix least-squares technique on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. The absolute structure was objectively determined by the refinement of the Flack parameter which was equal 0.035(13). The hydrogen atoms were placed in calculated positions and refined in riding mode with fixed thermal parameters. The final R factors were R_1 = 0.0340 for 1488 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.0772 for all 1854 independent reflections.

X-ray Crystal Structure Determination for 3e: Owing to the low melting point of the sample crystallization was performed by an in situ method. Liquid was sealed in a glass capillary with an inner diameter of 0.3 mm. The desired crystal of acceptable quality was grown close to the melting point. Afterwards the crystal with an outer liquid layer was slowly cooled to 100 K. The experiment was performed at a sample temperature equal to 100 K, which produced data for a twinned sample. The major domain of the twin was selected by the RLatt module of the APEX2 software.[11]

$C_{10}H_{10}NO$, M = 160.19, monoclinic, space group $P2_1/n$, 100 K, a = 10.249(3), b = 6.019(2), c = 15.492(4) Å, V = 90.947(7) Å^3, Z = 4 (Z' = 1), $d_{\text{calcd.}}$ = 1.113 g/cm^3, μ(Mo-K_α) = 0.73 cm^{-1}, $F(000)$ = 340. The intensities of 9837 reflections were measured with a Bruker SMART APEX2 diffractometer [λ(Mo-K_α) = 0.71072 Å, ω scans, $2\theta < 58°$] and were integrated by using the SAINT software.[12] A set of 2521 independent reflections [R_{int} = 0.0571] were used for further refinement. Absorption correction was applied semi-empirically with the SADABS software.[13] The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms were located by using the Fourier synthesis of electron density and refined in the isotropic approximation. Refinement converged to wR_2 = 0.0879 and GOF = 0.956 for all independent reflections [R_1 = 0.0424 was calculated against F for 1754 observed reflections with $I > 2\sigma(I)$].

All the calculations performed for **2b** and **3e** were carried out by using the SHELXTL PLUS program (PC Version 5.10).[14]

CCDC-679404 (for **2b**) and -696293 (for **3e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, ^{1}H/^{13}C NMR spectra for the prepared compounds, and X-ray data for compound **2b** and **3e**.

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