Tetrahedron: *Asymmetry* 21 (2010) 398–404

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Insights into the stereoselective BF_3-catalyzed hetero Diels–Alder reaction of Garner's aldehyde with Danishefsky's diene

Carolina Fontana [a], Marcelo Incerti [a], Guillermo Moyna [a,b], Eduardo Manta [a,*]

[a] *Cátedra de Química Farmacéutica, Departamento de Química Orgánica, Facultad de Química, Universidad de la República, Avenida General Flores 2124, Montevideo 11800, Uruguay*
[b] *Department of Chemistry & Biochemistry, University of the Sciences in Philadelphia, Philadelphia, PA 19104, USA*

ARTICLE INFO

Article history:
Received 23 December 2009
Accepted 23 February 2010

ABSTRACT

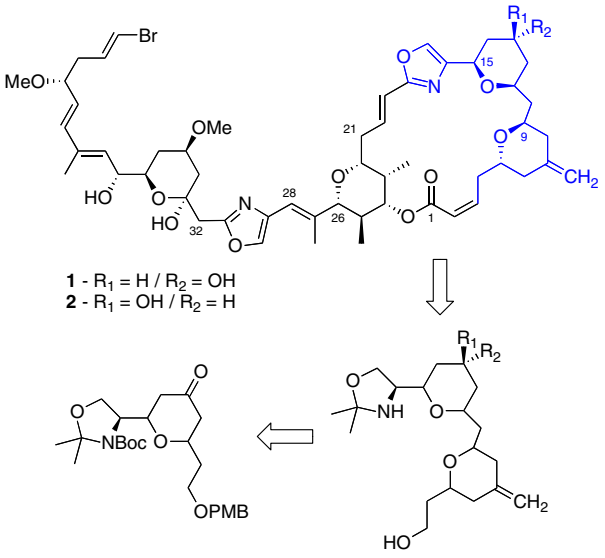
A *trans*-2,6-disubstituted tetrahydropyranone was prepared in high yield via a BF_3-mediated hetero Diels–Alder reaction between Danishefsky's diene and Garner's aldehyde. Only two of the four possible reaction products were obtained, and excellent diastereoselectivity toward the *exo–syn* adduct was observed (de = 80%). The origin of this somewhat unusual selectivity can be attributed to the steric interactions between the bulky protecting groups present in the diene and dienophile.

1. Introduction

Phorboxazoles **1** and **2** (Scheme 1), natural products first isolated by Searle and Molinski from the sponge *Phorbas* sp.,[1] display exceptional cytostatic activity against all 60 human tumor cell lines in the National Cancer Institute test panel, with an average IG_{50} below 0.9 nM. Recent studies with fluorescent phorboxazole derivatives indicate that these molecules induce persistent association between the extranuclear cytokeratin intermediate filaments (KRT10) and the cyclin-dependent kinase 4 (CDK4), leading to disruption of the cellular cycle at the G_1–S interphase.[2] This novel mechanism gives them enormous potential as antineoplastic agents, and could also complement and enhance the activity of mitotic spindle poisons that cause arrest between the G_2 and M phases, such as discodermolide, paclitaxel, and the epothilones.[3]

In addition to their antitumor activity and unique mechanism of action, the phorboxazoles present a variety of structural features that have inspired widespread interest among synthetic chemists and have led to several total and formal syntheses.[4] On the other hand, the number of structure–activity relationship (SAR) studies available for the phorboxazoles is relatively small.[5] Additional efforts in this area are required to fully decipher the mechanism of action of these molecules.

The synthesis of phorboxazole analogues suitable for SAR studies requires straightforward strategies for the preparation of several structural elements found in these molecules. As part of our ongoing efforts aimed toward the design of naturally inspired biologically active compounds through novel methodologies, we have recently detailed the synthesis and conformational evaluation of analogues of the C15–C32 bis-oxazole oxane fragment of the phorboxazoles.[6,7] Herein we report a high-yielding and stereoselective route for the preparation of key intermediates in the synthesis of analogues of the C3–C17 oxazole oxane fragment of these molecules (Scheme 1). The approach relies on the BF_3-catalyzed hetero Diels–Alder (HDA) reaction between Danishefsky's diene and Garner's aldehyde,[8,9] and leads to a *trans*-2,6-disubstituted tetrahydropyranone as the major product. Particular emphasis is made on the determination of the stereochemistry of the



Scheme 1. Chemical structure and numbering of phorboxazoles A (**1**, R^1 = H; R^2 = OH) and B (**2**, R^1 = OH; R^2 = H), and retrosynthetic analysis of the C3–C17 fragment.

* Corresponding author. Tel.: +598 2 924 1805; fax: +598 2 924 1906.
E-mail address: emanta@fq.edu.uy (E. Manta).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.02.028

products, which was achieved via a combination of spectroscopic and computational studies on the reaction products and rigid derivatives.

2. Results and discussion

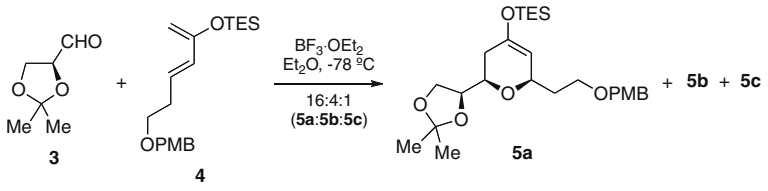
One of the first routes to the C3–C17 fragment of the phorboxazoles was reported by Cink and Forsyth more than a decade ago.[10] As depicted in Scheme 2, their strategy involved a BF_3-catalyzed HDA reaction between isopropylidene-(*S*)-glyceraldehyde **3** and TES-protected Danishefsky's diene **4**, which afforded **5a** as the major product of a 16:4:1 mixture of diastereomers. The outcome of the reaction was rationalized by the authors as the result of good Felkin selectivity and stabilization of the *endo* transition state through interactions of secondary orbitals.

Based on these results, and taking into account the well-documented use of Garner's aldehyde in similar stereocontrolled HDA cycloadditions,[9,11,12] we decided to investigate the suitability of oxazolidine **6** instead of acetonide **3** as the dienophile in the BF_3-catalyzed reaction. This route would lead to a precursor of the C3–C17 fragment bearing an oxazolidine ring on C-15, which, as we have recently shown,[7] can be readily converted into the oxazole moiety present in the parent compound. Thus, treatment of an ether solution of **6** and TBS-protected diene **7** with a catalytic amount of $BF_3{\cdot}OEt_2$ at −78 °C led exclusively to the formation of two of the four possible diastereomeric silyl enol ethers, compounds **8a** and **8b**, in 10:1 ratio (de = 80%) and an 82% combined yield. Following chromatographic separation of the two isomers, desilylation with TBAF in THF gave tetrahydropyranones **9a** and **9b** in 90% yield (Scheme 3).

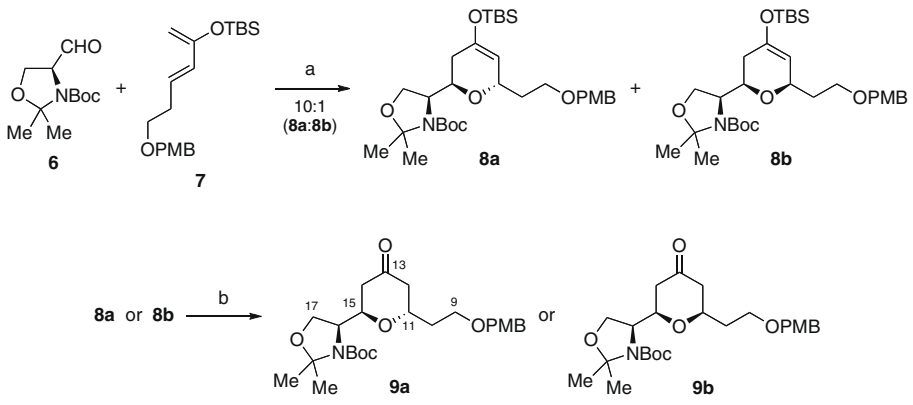
We relied on a combination of NMR experiments and molecular-modeling simulations to determine the stereochemistries of the two new stereogenic centers in compounds **9a** and **9b**. Following the assignment of ^1H and ^{13}C NMR resonances for both molecules (Tables 1 and 2), which was accomplished through interpretation of 1D and 2D (COSY, NOESY, HMBC, and HSQC) NMR data, an analysis of $^3J_{HH}$ coupling constants and NOE correlations was undertaken. A peculiar phenomenon observed with derivatives of Garner's oxazolidines is that their NMR spectra showed two sets of signals at 25 °C due to the slow dynamic equilibrium between conformers generated by rotation about the carbamate group C–N bond.[13] For this reason, most of the NMR experiments were performed at 60 °C, well above the coalescence temperature of the ^1H signal pairs. In the case of compound **9a**, both $^3J_{HH}$ couplings for H-11 are relatively small ($^3J_{H11-H12a}$ = 4.4 Hz and $^3J_{H11-H12b}$ = 6.0 Hz), suggesting that this proton is gauche to both protons on C-12, and consequently equatorial to the oxane ring. $^3J_{H14a-H15}$ and $^3J_{H14b-H15}$ vicinal coupling constants of 1.8 and 10.0 Hz, respectively, indicate that H-15 is gauche to H-14a, antiperiplanar to H-14b, and axial to the ring. The H-10a↔H-11 and H-10b↔H-15 NOESY correlations confirm an axial orientation for H-15 and the C-11 side chain (Table 1), and the large $^3J_{H11-H10b}$ (10.1 Hz) indicates an antiperiplanar arrangement of the H-11 and H-10b protons. These findings, summarized in Figure 1, are in agreement with a chair conformation for the oxane ring and a *trans* arrangement of its substituents. In addition, these data allowed us to tentatively assign the configuration of the C-11 and C-15 carbons as (*R*) and (*S*), respectively.

In order to obtain an accurate structural model for compound **9a** that could satisfactorily explain the NMR data presented above, the conformational space available to the molecule was thoroughly sampled using simulated annealing.[6,14] Apart from being an effective tool for the generation of large conformer ensembles, simulated annealing is particularly well suited to overcome the energy barriers that may preclude adequate sampling of the phase space in cyclic systems. The most populated family of conformers obtained following this approach, comprising of 50% of the low energy structures, corresponds with the chair conformation postulated earlier (Fig. 1d), and validates our preliminary model.

The same approach was followed in the structural study of compound **9b**. In this case, the large $^3J_{H14b-H15}$ (14.1 Hz) and $^3J_{H11-H12a}$ (11.6 Hz) coupling constants suggest that these protons have a

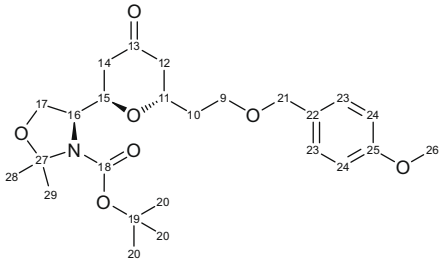


Scheme 2. BF_3-catalyzed HDA reaction of isopropylidene-(*S*)-glyceraldehyde **3** with Danisefsky's diene **4** reported by Cink and Forsyth.[8]



Scheme 3. BF_3-catalyzed HDA reaction of Garner's aldehyde **6** with Danisefsky's diene **7**. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, Et_2O, −78 °C, 82%; (b) TBAF, THF, 90%. The numbering scheme used for the C3–C17 fragment of the phorboxazoles is followed.

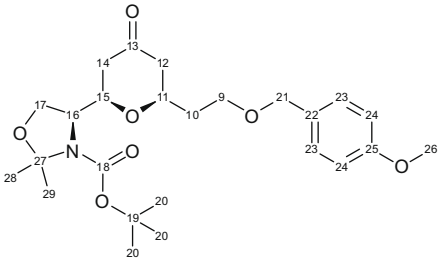
Table 1
^{1}H and ^{13}C NMR assignments and relevant NOE correlations for compound **9a** in $CDCl_3$ at 60 °C[a]



Position	^{1}H (ppm)	^{13}C (ppm)	NOE
9	3.54 (m, 2H)	66.1	H-10a (s), H-10b (s), H-11 (m)
10	1.74 (Ha, dddd, 14.2, 7.8, 5.2, 5.2, 1H) 1.91 (Hb, dddd, 14.2, 10.1, 5.2, 5.2, 1H)	33.4	H-9 (s), H-11 (s), H-12a (m) H-9 (s), H-15 (s)
11	4.51 (dddd, 10.1, 6.0, 5.2, 4.4, 1H)	70.9	H-9 (m), H-10a (s), H-12a (m), H-12b (s)
12	2.29 (Ha, dd, 15.0, 4.4, 1H) 2.67 (Hb, dd, 15.0, 6.0, 1H)	46.3	H-10a (m), H-11 (m) H-11 (s)
13	—	207.6	—
14	2.40 (Ha, dd, 14.0, 1.8, 1H) 2.58 (Hb, dd, 14.0, 10.0, 1H)	44.8	H-15 (s) —
15	4.03 (m, 1H)	71.1	H-10b (s), H-14a (s), H-28 (w)
16	4.03 (m, 1H)	60.8	—
17	3.86 (Ha, dd, 9.0, 5.2, 1H) 4.09 (Hb, d, 9.0, 1H)	64.8	H-29 (s) H-28 (w)
18	—	153.5	—
19	—	81.0	—
20	1.51 (s, 9H)	28.8	—
21	4.44 (s, 2H)	73.2	—
22	—	130.7	—
23	7.25 (d, 8.5, 2H)	129.7	—
24	6.89 (d, 8.5, 2H)	114.2	—
25	—	159.7	—
26	3.82 (s, 3H)	55.7	—
27	—	94.3	—
28	1.56 (s, 3H)	28.8	H-15 (w), H-17b (w)
29	1.54 (s, 3H)	28.8	H-17a (s)

[a] NOE correlations are classified as strong (s), medium (m), or weak (w).

Table 2
^{1}H and ^{13}C NMR assignments and relevant NOE correlations for compound **9b** in $CDCl_3$ at 60 °C[a]



Position	^{1}H (ppm)	^{13}C (ppm)	NOE
9	3.59 (m, 2H)	66.3	H-10a (s), H-10b (s)
10	1.84 (Ha, m, 1H) 1.94 (Hb, m, 1H)	36.8 —	— —
11	3.78 (m, 1H)	74.7	H-10a (m), H-10b (m), H-12b (m), H-15 (s)
12	2.28 (Ha, dd, 14.4, 11.6, 1H) 2.40 (Hb, m, 1H)	48.1	H-10a (m), H-10b (m) H-11 (m)
13	—	207.3	—
14	2.40 (m, 2H)	45.7	H-15 (s), H-17a (w), H-17b (w)
15	3.68 (dd, 14.1, 7.9, 1H)	77.6	H-11 (s), H-14 (s), H-17b (m), H-28 (w)
16	3.98 (m, 1H)	60.9	—
17	3.89 (Ha, dd, 8.9, 5.5, 1H) 4.07 (Hb, d, 8.9, 1H)	65.3	H-14 (w), H-29 (s) H-14 (w), H-15 (m), H-28 (w)
18	—	153.5	—
19	—	80.9	—
20	1.50 (s, 9H)	28.8	—
21	4.44 (s, 2H)	73.2	—
22	—	130.7	—
23	7.25 (d, 8.6, 2H)	129.6	—
24	6.90 (d, 8.6, 2H)	114.3	—
25	—	159.7	—
26	3.82 (s, 3H)	55.6	—
27	—	94.3	—
28	1.56 (s, 3H)	28.1	H-15 (w), H-17b (w)
29	1.54 (s, 3H)	28.1	H-17a (s)

[a] NOE correlations are classified as strong (s), medium (m), or weak (w).

trans 1,2-diaxial arrangement (Fig. 2). Together with the strong H-11↔H-15 NOESY correlation (Table 3), these data are in agreement with a *cis*-configuration of the oxane ring, and are also consistent with (*R*)-configurations of both the C-11 and C-15 carbons.

A detailed structural model for compound **9b** was also obtained using simulated annealing. In this case, all the low energy conformers generated with this protocol corresponded with the chair conformation postulated earlier (Fig. 2d). As for **9a**, these simulations corroborate our initial stereochemical assignments.

To further confirm the configuration of the stereogenic centers in compound **9b**, we set out to prepare a rigid derivative with no rotation around the C-15–C-16 bond. This would allow the configuration of the C-16 carbon, originating from L-serine, to be used directly as reference to establish the stereochemistries of the newly created stereogenic centers. This transformation was accomplished by a series of steps summarized in Scheme 4. First, the treatment of the *cis*-tetrahydropyranone with $NaBH_4$ yielded an equatorial alcohol as a result of the axial attack of the reducing agent on the C-13 ketone group.[15] Following acetylation of this alcohol and acid-catalyzed removal of the isopropylidene moiety, the C-17 hydroxyl group was oxidized to the carboxylic acid using aqueous $NaClO_2$ and a catalytic amount of TEMPO and NaClO. The C-13 alcohol was then deacetylated, and the resulting hydroxy-acid lactonized to give bicycle **10**. In this compound, the C-15–C-16 bond is fixed, making it ideal for our purposes.

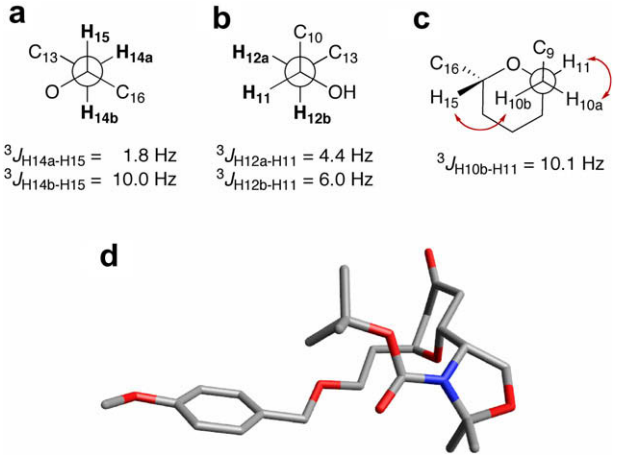


Figure 1. Coupling constant analysis for protons H-15 (a), H-11 (b), and H-10b (c), relevant NOE correlations (in red), and heavy atom representation of the most populated conformer family obtained for compound **9a** through simulated annealing (d).

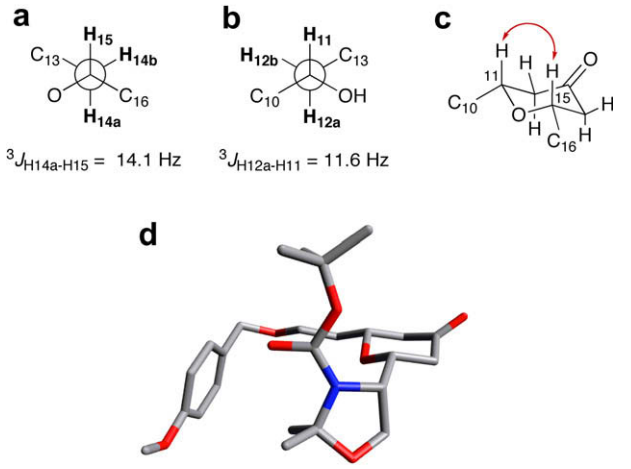


Figure 2. Coupling constant analysis for protons H-11 (a), H-15 (b), proposed chair conformation showing relevant NOE correlations (c), and heavy atom representation of the most populated conformer family obtained for compound **9b** through simulated annealing (d).

The stereochemistry of compound **10** was then studied using 1D-NOESY experiments. The strong dipolar coupling between H-11 and H-14b, together with the medium H-11↔H-15 correlation (Fig. 3b and c), indicates that the oxane ring adopts a boat conformation (Fig. 4d). This is also corroborated when the relative intensities of these two NOE correlations are qualitatively compared with the internuclear distances between these protons. These observations are also in agreement with a *cis*,*cis* arrangement of the C-13, C-15, and C-16 substituents on the lactone ring. Finally, the NOE observed between H-14a and H-16 (Fig. 3a) allowed us to confirm the absolute configuration of the C-11 and C-15 stereogenic centers proposed previously.

The conclusions derived from NOE data are also consistent with the results obtained from the analysis of the vicinal coupling constants. The $^3J_{H11-H12a}$ and $^3J_{H11-H12b}$ of 10.6 and 5.3 Hz, respectively, indicate that H-11 is gauche to H-12a, antiperiplanar to H-12b, and thus axial to the oxane ring (Fig. 4a). The $^3J_{HH}$ couplings for H-15 with both protons on C-14 are either small or undetectable ($^3J_{H15-H14b}$ = 5.6 Hz and $^3J_{H15-H14a} \sim 0$), suggesting that this proton is gauche to both protons on C-14 and consequently equatorial to the oxane ring (Fig. 4b). Similarly, the coupling constants for H-13 with protons H-12a, H-12b, H-14a, and H-14b are small and could not be detected experimentally, revealing that this proton is gauche to protons on both C-12 and C-14 and also equatorial to the oxane ring (Fig. 4c).

While the rigidity of **10** drastically reduces the number of conformations that this compound can adopt, an accurate structural model was obtained following the same approach employed for **9a** and **9b**. The single conformer obtained is supported by the observed NOE correlations. Furthermore, $^3J_{HH}$ coupling constants back-calculated from this structure using the Haasnoot-de Leeuw-Altona equation agree remarkably well with the experimental values (Table 3).[16]

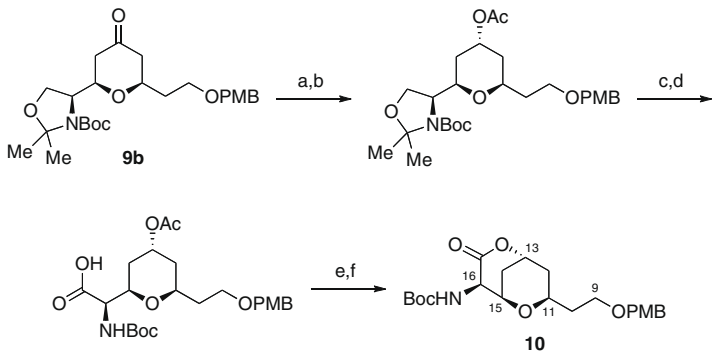
The results described above allow us to draw conclusions regarding the stereochemical outcome of the HDA reaction. First, and in analogy to what was observed by Cink and Forsyth in the cycloaddition of **3** with **4**,[10] Lewis acid chelation is precluded and good Felkin control was achieved, leading only to the observed *syn* products. Conversely, while the use of acetonide **3** led to an *endo* adduct (*cis* product), the reaction with Garner's aldehyde **6** affords almost exclusively an *exo* adduct (*trans* product). Although this selectivity is somewhat uncommon, it can be satisfactorily explained in terms of steric interactions between the –NBoc- and –OTBS-protecting moieties present on oxazolidine **6** and diene **7** that would destabilize the *endo* transition state (Scheme 5).

Table 3
Experimental and back-calculated $^3J_{HH}$ coupling constants for compound **10**

Proton pair	Calculated dihedral angles (°)	Back-calculated $^3J_{HH}$ (Hz)	Experimental $^3J_{HH}$ (Hz)
H-16–H-15	−57	2.5	1.6
H-15–H-14a	75	0.6	~0
H-13–H-14b	−44	6.1	5.6
H-13–H-14a	−56	4.2	4.6
H-13–H-14b	62	1.6	~0
H-13–H-12a	96	0.7	~0
H-13–H-12b	−21	7.9	7.1
H-11–H-12a	−163	11.2	10.6
H-11–H-12b	−45	4.2	5.3

3. Conclusions

In conclusion, we have presented a straightforward route to 2,6-disubstituted tetrahydropyranones, key fragments in the preparation of analogues of the C3–C17 oxazole oxane fragment of the phorboxazoles. It is worth noting that despite being highly stereoselective, our approach leads to a tetrahydropyranone with a *trans* stereochemistry not found in the natural product. In principle, the correct stereoisomer could be obtained using a chelating Lewis acid such as $ZnCl_2$ and Garner's aldehyde derived from D-serine as dienophile. Attack from the *re*-face of the oxazolidine-catalyst complex would situate the –NBoc and –OTBS groups far from each other in this case, thus not hindering the formation of the expected



Scheme 4. Preparation of bicyclic lactone **10**. Reagents and conditions: (a) $NaBH_4$, MeOH; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 75% (both steps); (c) $TsOH{\cdot}H_2O$, dioxane; (d) TEMPO, $NaClO_2$, NaClO, phosphate buffer, MeCN, 53%; (e) $NaBH_4$, MeOH; (f) EDCI, DMAP, CH_2Cl_2, 21% (both steps).

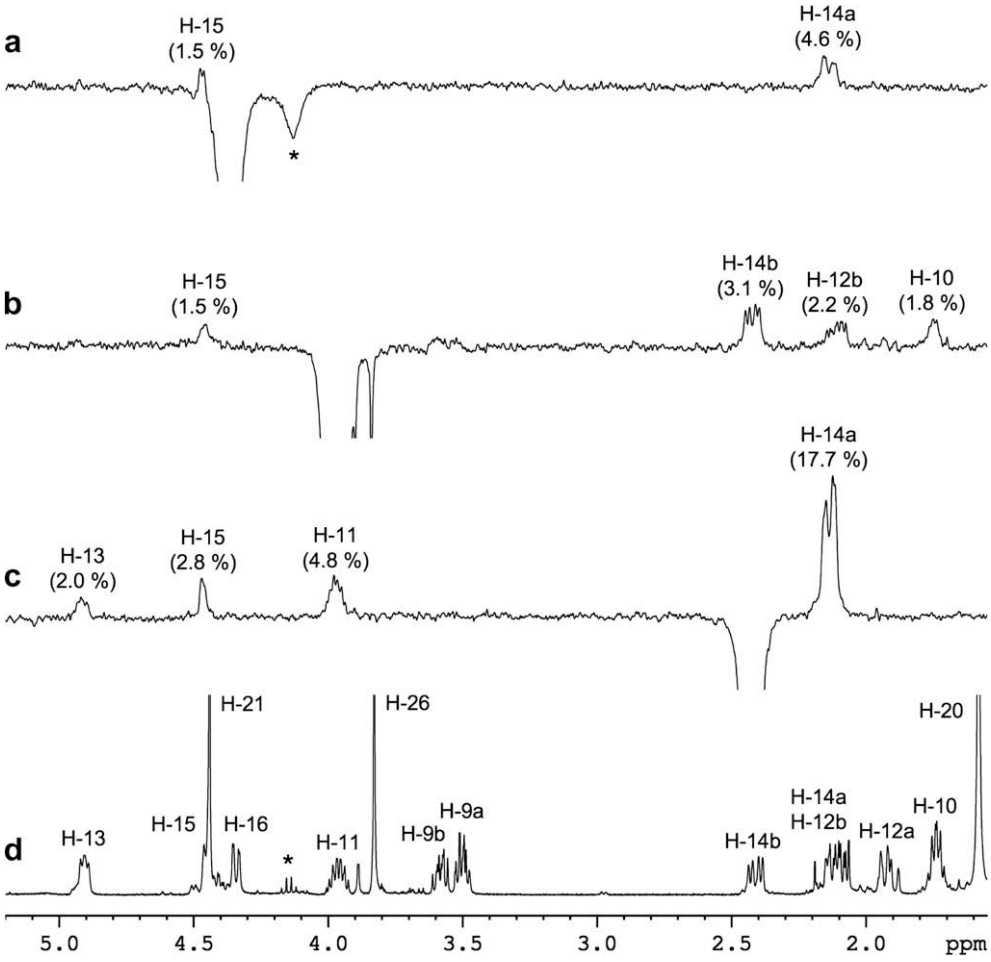


Figure 3. 1D-NOE spectra obtained for lactone **10** after selective inversion of protons H-16 (a), H-11 (b), and H-14b (c). The standard ^{1}H NMR spectrum is shown for reference (d). The (*) indicates an impurity in the sample.

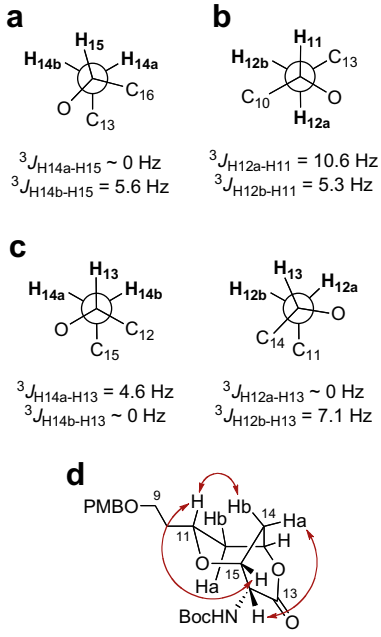


Figure 4. Coupling constant analysis for protons H-15 (a), H-11 (b), and H-13 (c), and proposed bicycle conformation for compound **10** showing relevant NOE correlations (d).

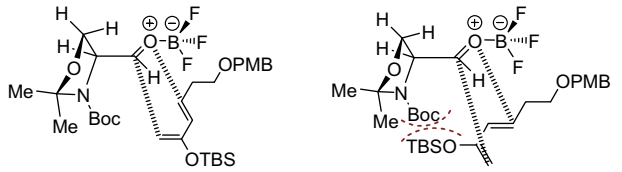
endo–syn transition state (Scheme 6). Work on this hypothesis is currently ongoing and our findings will be reported in due course.

4. Experimental

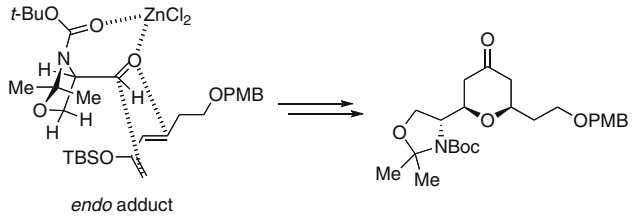
4.1. General

Flash column chromatography purifications were carried out using 230–400 mesh silica gel. Optical rotations were measured on Perkin–Elmer 341 and Krüss Optronic P8000 polarimeters equipped with 1.0 and 0.5 mL cells, respectively. IR spectra were recorded on a Shimadzu 8101 FT-IR spectrophotometer. MS and HRMS spectra were recorded on Shimadzu GC–MS QP 1100 EX and VG AutoSpec Q mass spectrometers, respectively, using electron impact ionization in both cases. NMR experiments were carried out on a Bruker AVANCE 400 spectrometer equipped with a 5 mm QXI probe and operating at ^{1}H and ^{13}C frequencies of 400.13 and 100.61 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual $CDCl_3$ signal (7.28 ppm), and couplings constants (J) are given in hertz. 1D-NOESY experiments were performed with the DPFGSE-NOE pulse sequence of Stott and co-workers,[17] using Gaussian-shaped pulses for selective proton inversion. A mixing time of 500 ms was employed for all 1D and 2D NOESY experiments.

Molecular modeling studies were carried out using HyperChem 7.52 (HyperCube, Inc.). The low-energy conformers for compound



Scheme 5. Transition states leading to the observed *syn* HDA reaction products **8a** and **8b**. Steric clashes between the –NBoc and –OTBS groups that can potentially destabilize the *endo* adduct are shown.



Scheme 6. Proposed *endo–syn* transition state for the $ZnCl_2$-mediated HDA with Garner's aldehyde derived from D-serine as dienophile.

9a, **9b**, and **10** were generated with a simulated annealing protocol.[6,14] The MM2-based MM+ force field was employed for the simulations,[18] using no non-bonded cutoffs and bond dipoles to compute electrostatic interactions. Each simulated annealing cycle consisted of 1 ps of equilibration at 800 K and annealing to 200 K for a 0.8 ps period, followed by minimization of the resulting structures to an energy gradient below 0.001 Kcal/mol. From the total 1000 structures obtained through this process, a set of 50 low-energy conformers was selected for the analyses detailed above.

4.2. Preparation of silyl enol ethers 8a and 8b

$BF_3{\cdot}OEt_2$ (183 μL, 1.5 mmol) was added to a solution of **6** (3.43 g, 15.0 mmol) and **7** (4.64 g, 13.3 mmol) in Et_2O (90 mL) at −78 °C, and the resulting mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (10 mL), the mixture was diluted with EtOAc (120 mL), and washed with H_2O (40 mL) and brine (50 mL). The aqueous layer was subsequently extracted with EtOAc (2 × 25 mL), and the combined organic layers were dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The resulting yellow oil was purified by flash chromatography with silica gel previously neutralized with triethylamine (EtOAc/hexanes, 1:5) to afford silyl enol ethers **8a** and **8b** in a 10:1 ratio (6.3 g, 82% combined yield).

4.2.1. (*S*)-*tert*-Butyl 4-((2*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)-3,6-dihydro-2*H*-pyran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 8a

Obtained as a colorless oil. R_f = 0.60 (EtOAc/hexanes 1:6). IR ($CHCl_3$, cm^{-1}): 2934, 2859, 1797, 1613, 1514, 1474, 1310, 1252, 1204, 1175, 1096, 1053, 835. ^1H NMR (60 °C): δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.82 (s, 1H), 4.48 (m, 1H), 4.44 (s, 2H), 4.07 (d, *J* = 8.1 Hz, 1H), 4.04 (m, 1H), 3.95 (m, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.57 (m, 2H), 2.23 (m, 1H), 1.90 (m, 2H), 1.90 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H), 1.15 (s, 9H), 0.93 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (60 °C): δ 159.6, 152.0, 148.1, 131.0, 129.6 (2), 114.2 (2), 106.2, 94.5, 80.5, 73.2, 73.1, 70.4, 70.2, 67.3, 60.4, 55.6, 45.3, 35.1, 28.8 (3), 26.0, 18.4, –4.2 (2). MS *m*/*z* (rel. int.): 577 ($[M]^+$, 1), 504 (7), 478 (6), 456 (13), 400 (16), 377 (16), 328 (5), 137 (8), 121 (100), 100 (17), 75 (8), 57 (23). HRMS: *m*/*z* calcd for $C_{31}H_{51}NO_7Si$: ([M]+): 577.3435, found 577.3406.

4.2.2. (*S*)-*tert*-Butyl 4-((2*S*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)-3,6-dihydro-2*H*-pyran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 8b

Obtained as a colorless oil. R_f = 0.65 (EtOAc/hexanes 1:6). IR ($CHCl_3$, cm^{-1}): 2934, 2859, 1796, 1613, 1514, 1464, 1366, 1252, 1173, 1098, 1038, 837, 777. ^1H NMR (60 °C): δ 7.28 (d, *J* = 8.7, 2H), 6.88 (d, *J* = 8.7, 2H), 4.77 (s, 1H), 4.44 (s, 2H), 4.30 (m, 1H), 4.06 (d, *J* = 9.2), 3.88 (m, 1H), 3.86 (m, 1H), 3.82 (s, 3H), 3.68 (m, 1H), 3.57 (m, 2H), 2.22 (m, 1H), 1.91 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.47 (s, 9H), 0.93 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (60 °C): δ 159.6, 152.7, 149.3, 131.0, 129.6 (2), 114.2 (2), 106.8, 89.1, 80.5, 74.5, 73.1, 72.1, 66.9 (2), 60.6, 55.6, 44.8, 37.0, 28.8 (3), 26.0, 18.4, −3.9 (2). MS *m*/*z* (rel. int.): 577 ($[M]^+$, 1), 504 (7), 478 (6), 456 (13), 400 (16), 377 (16), 328 (5), 137 (8), 121 (100), 100 (17), 57 (23). HRMS: *m*/*z* calcd for $C_{31}H_{51}NO_7Si$: ($[M]^+$): 577.3435, found 577.3400.

4.3. Preparation of tetrahydropyranones 9a and 9b

A solution of silyl enol ether **8a** (6.58 g, 11.4 mmol) in THF (90 mL) at 0 °C was treated with a 1 M solution of TBAF in THF neutralized with $TsOH{\cdot}H_2O$ (11.4 mL). The resulting mixture was stirred for 10 min and diluted with Et_2O (150 mL). The organic layer was then washed with H_2O (2 × 70 mL), brine (70 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (EtOAc/hexanes, 1:2) to give **9a** in 90% yield (4.75 g). Tetrahydropyranone **9b** was obtained from **8b** following an analogous procedure.

4.3.1. (*S*)-*tert*-Butyl 4-((2*R*,6*S*)-6-(2-(4-methoxybenzyloxy)ethyl)-4-oxo-tetrahydro-2*H*-pyran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 9a

Obtained as a colorless oil. R_f = 0.50 (EtOAc/hexanes, 1:2). $[\alpha]_D^{20} = -42.7$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3006, 2979, 2870, 1720, 1613, 1514, 1457, 1308, 1250, 1173, 1098, 758. ^1H and ^{13}C NMR: see Table 1. ^{13}C NMR: see Table 1. MS *m*/*z* (rel. int.): 462 ($[M+H]^+$, 1), 406 (10), 364 (7), 200 (6), 144 (8), 121 (100), 100 (32), 57 (40). HRMS: *m*/*z* calcd for $C_{25}H_{37}NO_7$ 462.2492 ($[M+H]^+$), found 462.2646.

4.3.2. (*S*)-*tert*-Butyl 4-((2*R*,6*R*)-6-(2-(4-methoxybenzyloxy)ethyl)-4-oxo-tetrahydro-2*H*-pyran-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 9b

Obtained as a colorless oil, R_f = 0.50 (EtOAc/hexanes, 1:2), $[\alpha]_D^{20} = -27.9$ (*c* 1.0, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): 3007, 2940, 2875, 1717, 1698, 1517, 1387, 1306, 1248, 1173, 759. ^1H and ^{13}C NMR: see Table 2. MS *m*/*z* (rel. int.): 462 ($[M+H]^+$, 1), 406 (20), 364 (7), 144 (6), 137 (7), 121 (100), 57 (37). HRMS: *m*/*z* calcd for $C_{25}H_{37}NO_7$ 462.2492 ($[M+H]^+$), found 462.2481.

4.4. Preparation of bicyclic lactone 10

$NaBH_4$ (23 mg, 0.61 mmol) was added in portions to a solution of **9b** (235 mg, 0.51 mmol) in MeOH (5 mL) at 0 °C. The mixture was stirred for 30 min, diluted with water (10 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude alcohol was resuspended in CH_2Cl_2 (12 mL) and treated with Ac_2O (69 μL, 0.73 mmol), pyridine (57 μL, 0.73 mmol), and a catalytic amount of DMAP. The mixture was stirred for 1 h, diluted

with water (10 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (EtOAc/hexanes, 1:2) gave the corresponding acetate in 75% yield (190 mg).

The above product (175 mg, 0.35 mmol) was dissolved in dioxane (6 mL) and treated with *p*-TsOH·H_2O (19 mg, 0.10 mmol). The mixture was then diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure. A solution of this crude primary alcohol (40 mg, 0.086 mmol) in MeCN (0.5 mL) and phosphate buffer (0.67 M, pH 6.7, 0.35 mL) was heated to 35 °C and treated with TEMPO (1 mg). This was followed by the simultaneous addition of aqueous solutions of $NaClO_2$ (20 mg in 0.1 mL) and NaOCl (2 mg in 0.05 mL). The resulting mixture was stirred at 35 °C until the starting material was consumed, and then cooled to RT. Water (0.5 mL) and 2 M NaOH (0.05 mL) were added, and the reaction was then quenched by pouring into a Na_2SO_3 solution. The mixture was acidified to pH 3-4 with 5% HCl and extracted with EtOAc (3 × 5 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude acid in 53% yield (20 mg).

The material obtained from the previous steps (20 mg, 0.043 mmol) was dissolved in MeOH (5 mL) and treated with $NaBH_4$ in portions until deacetylation was confirmed by TLC. Water (5 mL) was then added, and the mixture was extracted with EtOAc (3 × 5 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Without purification, the resulting crude hydroxyacid (18 mg, 0.043 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with EDCI (16 mg, 0.086 mmol) and a catalytic amount of DMAP at 0 °C. Following consumption of the starting material brine (1 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 2 mL). The organic layer was dried with $MgSO_4$, the solvent removed under vacuum, and the crude oil purified by flash chromatography (EtOAc/EP, 2:1) to afford **10** as a colorless oil in 21% yield (4 mg).

4.4.1. *tert*-Butyl (1*S*,4*R*,5*R*,7*R*)-7-(2-(4-methoxybenzyloxy)ethyl)-3-oxo-2,6-dioxa-bicyclo[3.3.1]nonan-4-ylcarbamate 10

R_f = 0.50 (EtOAc/hexanes, 2:1). $[\alpha]_D^{20} = +10.6$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (30 °C): δ 5.36 (d, *J* = 8.7, 1H), 7.26 (d, *J* = 8.6, 2H), 6.90 (d, *J* = 8.6, 2H), 4.91 (dd, *J* = 7.1, *J* = 4.6, 1H), 4.46 (dd, *J* = 5.6, *J* = 1.6, 1H), 4.44 (s, 2H), 4.35 (dd, *J* = 8.7, *J* = 1.6, 1H), 3.97 (dddd, *J* = 10.6, *J* = 6.9, *J* = 5.3, *J* = 5.3, 1H), 3.83 (s, 3H), 3.59 (m, 1H), 3.52 (m, 1H), 2.42 (dd, *J* = 14.1, *J* = 5.6, 1H), 2.14 (dd, *J* = 14.1, *J* = 4.6, 1H), 2.10 (ddd, *J* = 15.5, *J* = 7.1, *J* = 5.3, 1H), 1.92 (dd, *J* = 15.5, *J* = 10.6, 1H), 1.74 (m, 2H), 1.50 (s, 9H). ^{13}C NMR: δ 170.8, 159.7, 156.1, 130.8, 129.7 (2), 114.2 (2), 80.9, 73.8, 73.1, 69.3, 66.2, 65.9, 58.7, 55.7, 39.0, 36.5, 28.7 (3), 27.3. HRMS: *m*/*z* calcd for $C_{22}H_{31}NO_7$ 422.2173 ($[M+H]^+$), found 422.2187.

Acknowledgments

We acknowledge the Facultad de Química, the Programa de Desarrollo de las Ciencias Básicas and the Fondo Clemente Estable (Grant FCE/2004/10050) for financial support (C.F., M.I., E.M.). G.M. recognizes funding from the Agencia Nacional de Investigación e Innovación, the Camille and Henry Dreyfus Foundation (Award TH-08-004), the Comision Sectorial de Investigación Científica, and the Royal Society of Chemistry. We also wish to thank Professor Graciela Mahler for insightful discussions.

References

1. (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126; (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422; (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.
2. Forsyth, C. J.; Ying, L.; Chen, J.; La Clair, J. J. *J. Am. Chem. Soc.* **2006**, *128*, 3858.
3. Hearn, B. R.; Shaw, S. J.; Myles, D. C.. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D. J., Eds.; Elsevier Science: Oxford, 2006; Vol. 7, pp 81–110.
4. (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597; (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033; (c) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536; (d) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834; (e) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942; (f) Gonzalez, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255; (g) Williams, D. A.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258; (h) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173; (i) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399; (j) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, C.; Zhou, W.-S.; Lin, G.-Q. *Chem. Eur. J.* **2006**, *12*, 1185; (k) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039; (l) White, J. D.; Lee, T. H.; Kuntiyong, P. *Org. Lett.* **2006**, *8*, 6043; (m) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769; (n) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T.; Meis, R. M. *J. Org. Chem.* **2008**, *73*, 1192.
5. (a) Uckun, F. M.; Forsyth, C. *J. Bioorg. Med. Chem. Lett.* **2001**, *11*, 1181; (b) Uckun, F. M. *Curr. Pharm. Des.* **2001**, *7*, 1627; (c) Hansen, T. M.; Engler, M. M.; Forsyth, C. *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 2127; (d) Smith, A. B., III; Razler, T. M.; Pettit, G. R.; Chapuis, J.-C. *Org. Lett.* **2005**, *7*, 4403; (e) Smith, A. B.; Razler, T. M.; Meis, R. M.; Pettit, G. R. *Org. Lett.* **2006**, *8*, 797; (f) Chen, J.; Ying, L.; Hansen, T. M.; Engler, M. M.; Lee, C. S.; La Clair, J. J.; Forsyth, C. *J. Bioorg. Med. Chem. Lett.* **2006**, *16*, 901; (g) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *J. Org. Chem.* **2008**, *73*, 1201.
6. Fontana, C.; Incerti, M.; Moyna, G.; Manta, E. *Magn. Reson. Chem.* **2007**, *46*, 36.
7. Incerti, M.; Fontana, C.; Scarone, L.; Moyna, G.; Manta, E. *Heterocyles* **2008**, *75*, 1385.
8. Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
9. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.
10. Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672.
11. Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.
12. Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **2002**, *67*, 598.
13. Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Tetrahedron* **2003**, *59*, 5713.
14. Moyna, G.; Williams, H. J.; Scott, A. I.; Ringel, I.; Gorodetsky, R.; Swindell, C. S. *J. Med. Chem.* **1997**, *40*, 3305.
15. Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
16. (a) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783; (b) Altona, C. In *Encyclopedia of Nuclear Magnetic Resonance*; Grant, D. M., Harris, R. K., Eds.; John Willey & Sons: New York, 1996; pp 4909–4922.
17. Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302.
18. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.