1α,25-Dihydroxyvitamin D_3 A-Ring Precursors: Studies on Regioselective Enzymatic Alkoxycarbonylation Reactions of Their Stereoisomers. Chemoenzymatic Synthesis of A-Ring Synthon Carbamate Derivatives, Including Carbazates and Polyamino Carbamates

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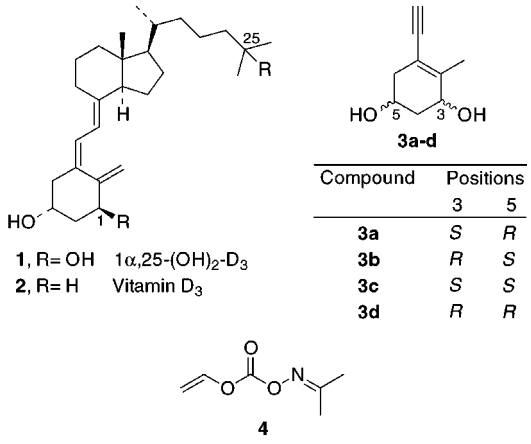
The stereoisomers of 1α,25-dihydroxyvitamin D_3 A-ring synthon **3a**, named **3b**−**d**, were subjected to a very comprehensive regioselective enzymatic study with *Candida antarctica* lipase (CAL). From this, it emerged that **3b**, the enantiomer of the natural A-ring synthon, was a very good substrate for CAL in toluene, dioxane, or THF, showing in all cases conversions close to 100% and regioselectivities between 95% and 99% toward the C-5-(*S*) hydroxyl group. The best results for the regioselective enzymatic transformation of stereoisomer **3c** were achieved with toluene at 30 °C or with THF at 60 °C. The regioselectivity displayed a preference toward the C-5-(*S*) hydroxyl group. The 1:10 ratio (**3c**:**4**) was mandatory so as to obtain an acceptable degree of conversion (in dioxane or THF). The A-ring synthon **3d** has a surprising conduct, suffering C-5-(*R*) enzymatic alkoxycarbonylation, whereas in the acylation process with *Chromobacterium viscosum* lipase, it showed behavior opposite to that observed for **3a**−**c**. In addition to the above, an efficient chemoenzymatic synthesis of A-ring synthon carbamate derivatives **15a,c**−**17a,c**, including carbazates **15b**−**17b**, and polyamino carbamates **15d**−**17d** was accomplished by a two-step strategy, involving the regioselective enzymatic synthesis of carbonates **5**, **7**, and **10**, followed by reaction with (poly)amino derivatives **14**.

Introduction

Biocatalysis in organic media has been the aim of intensive basic and application-oriented research. In these processes enzymes are used as catalysts, and lipases in particular have received the most attention because they are one of the most versatile classes of biocatalysts in organic synthesis.[1] The preparation of optically active products via enzyme-mediated reactions has demonstrated impressively the usefulness of these catalysts.[2] Just as with enantioselectivity, the ability of the enzymes to catalyze the regioselective modification of several functional groups is also of great interest for organic synthesis.[3] Over the past few years, a biotransformation has sometimes proven to be the key step in the synthesis of biologically active natural products and their analogues.[4]

1α,25-Dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3] (**1**, Chart 1), the hormonally active metabolite of vitamin D_3 (**2**), has, in addition to its classical role in calcium homeostasis, a broad spectrum of activities such as cell differentiation and immunomodulation. The latter have been utilized to develop therapeutic agents for cancer, bone, kidney, and skin diseases, neurological disorders (Alzheimer's disease), and AIDS.[5] A majority of analogues synthesized are altered in the side chain; modifications of the A-ring are less extensive, although A-ring analogues exhibit a unique biological profile. The reason is probably the more complicated synthetic routes required to obtain the appropriate A-ring precursors.[6] In our research directed toward the preparation of A-ring synthons, we previously synthesized carbamate derivatives of the natural A-ring of 1α,25-$(OH)_2$-D_3 by applying a two-

Chart 1



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step chemoenzymatic strategy.[7] This synthon possesses two hydroxyl groups of similar reactivity, and as a result it is very difficult to discern between these two groups from the chemical point of view. Using the methodology of enzymes in organic solvents it is possible to selectively modify only one of them, as has been similarly shown in nucleoside chemistry.[8]

Here we report a systematic study of the regioselective enzymatic alkoxycarbonylation of A-ring stereoisomers **3**. Whereas transesterification reactions have been extensively studied, the alkoxycarbonylation reaction has been poorly investigated.[2−4] Besides their own significance, we also use these carbonates as intermediates for the introduction of other functional groups such as carbazates and carbamates. Furthermore, the latter would provide very interesting derivatives as polyamine carbamates, since polyamines display a variety of important biological activities, affecting DNA replication and translation, protein synthesis, membrane stabilization, and the activity of certain kinases and topoisomerases.[9] For example, polyamine carbamate analogues of cholesterol have potential application as cationic liposomes for gene delivery in gene therapy.[10]

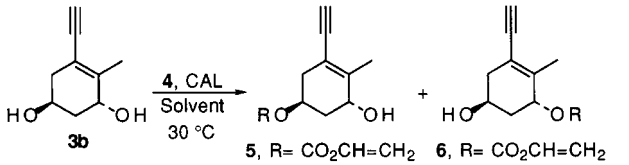
Results and Discussion

Since it has been demonstrated that enzymatic acylation of A-ring synthons **3a**−**d** gives a surprising selectivity depending on the A-ring stereoisomer used,[11] further evaluation of these, together with an interpretation of new results related to enzymatic catalysis, awaits the completion of studies. In the case of acylation, *Chromobacterium viscosum* lipase (CVL) selectively catalyzes the acylation of the C-5 hydroxyl of the three stereoisomeric vitamin D A-ring precursors **3a**−**c**, but only the C-3 hydroxyl of the fourth stereoisomer **3d** is acylated under the same conditions in organic solvents. However, studies on enzymatic alkoxycarbonylation focused on the A-ring fragment **3a**,[7] which possesses the natural enyne stereochemistry (3*S*,5*R*). *Candida antarctica* lipase (CAL) was found to be the best catalyst in toluene. Regioselective alkoxycarbonylation occurred only at the C-5-(*R*) hydroxyl group, as would be expected from previous experience. It is noteworthy that no C-3-(*S*) carbonate was obtained.[11]

To more fully investigate the latter process, a complete study was performed with two goals in mind. The first was to understand the enzyme selectivity both for this alkoxycarbonylation reaction and for the enzymatic acylation to be able to predict their behavior when applied to synthesis. The second goal was to prepare new A-ring synthons of 1α,25-$(OH)_2$-D_3, an area of great expansion in recent years[12] and one of our research topics.[7,11,13]

As previously mentioned, the best conditions for alkoxycarbonylation were using CAL−toluene as the enzyme solvent system at 30 °C, although CAL−THF (at 60 °C) and CAL−dioxane (at 30 °C) gave conversions greater than 80% of C-5 carbonates. The alkoxycarbonylating reagent used was acetone *O*-[(vinyloxy)carbonyl]oxime **4** (Chart 1) because of its synthetic utility to easily form carbamates (which include amine, alcohol, or amino acid functions in their alkyl moiety) from carbonates in mild reaction conditions.

Table 1. Regioselective Enzymatic Alkoxycarbonylation of 3b with 4



entry	solvent	ratio[a]	*t* (h)	conv (%)[b]	**5** (%)[b,c]	**6** (%)[b,c]
1	toluene	1:10	1	100	99	1
2	toluene	1:4	2	100	97	3
3	toluene	1:2	2	100	95	5
4	1,4-dioxane	1:10	26	96	92	4
5	1,4-dioxane	1:4	10	97	92	5
6	1,4-dioxane	1:2	10	98	94	4
7	THF	1:10	32	98	93	5
8	THF	1:4	22	98	93	5
9	THF	1:2	23	99	96	3

[a] Ratio between **3b** and **4**. [b] Calculated by GC. [c] Percentage of product formation.

With the aim of comparing the different behavior of the stereoisomers of **3a** and checking the influence of the stereochemistry of the different centers in the enzymatic alkoxycarbonylation process with CAL, we have used three solvents (1,4-dioxane, toluene, and THF), different ratios of alkoxycarbonylation reagent **4**, and several temperatures. Thus, first, the alkoxycarbonylation of stereoisomer **3b** was performed with CAL in toluene at 30 °C and using a ratio of diol **3b** to carbonate **4** of 1:10. In these conditions the process was immediate, as shown by gas chromatography (GC) analysis of the reaction solution (although it will be observed that part of diol **3b** was still insoluble on the walls of the Erlenmeyer), but the end of the reaction was marked by the complete solubility of the diol **3b** in toluene, which took place in approximately 1 h. This process showed an excellent regioselectivity (99%) (entry 1, Table 1) toward the C-5-(*S*) hydroxyl group. With the purpose of using less alkoxycarbonylating reagent, we ran 1:4 and 1:2 (**3b**:**4**) processes. It was observed that the starting material took more time to dissolve (2 h) than before, which is in agreement with all of our efforts to previously dissolve the diol **3b** in toluene before adding the enzyme and

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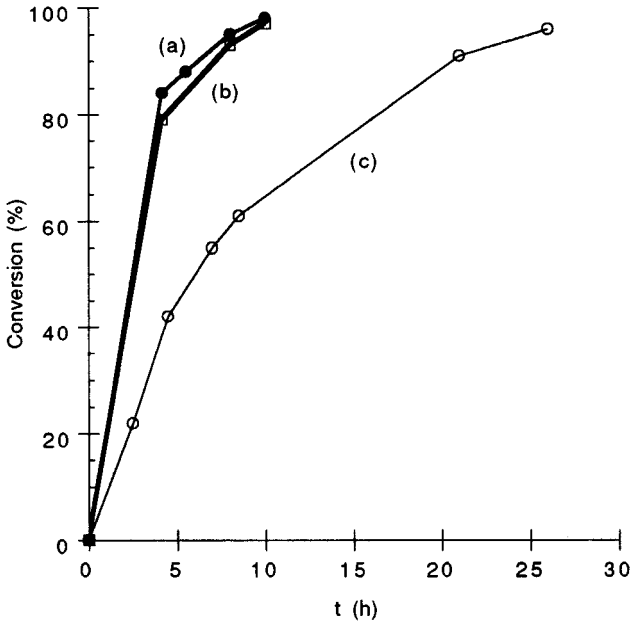


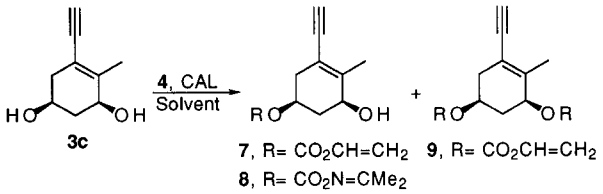
Figure 1. Enzymatic alkoxycarbonylation in 1,4-dioxane of diol **3b** with carbonate **4** catalyzed by CAL at different ratios between **3b** and **4**: (a) 1:2, (b) 1:4, and (c) 1:10.

carbonate **4**. This means that carbonate **4** helps to dissolve the diol **3b** in toluene. In both processes, the enzyme keeps the high regioselectivity, as shown by entries 2 and 3 in Table 1. In the case of entry 1, after purification of compound **5** by flash chromatography, the excess of carbonate **4** was recovered.

Despite the fact that enzymes normally work better in apolar than in polar organic solvents, we tried to use 1,4-dioxane or THF to facilitate the solubility of diol **3b**. Although the solubility of **3b** was increased using dioxane, the reaction times were longer than in toluene. As can be seen in Table 1 (entries 4−6), the enzyme showed an appreciable inhibition when the ratio of carbonate **4** was increased. This inhibition is evident in Figure 1, in which the percentage of conversion at different times is plotted. Thus, curves (a) and (b), corresponding to ratios 1:2 and 1:4, respectively, are very similar, and in approximately 10 h the reactions were complete with 97−98% conversion. In contrast, 26 h were necessary to obtain 96% conversion when the ratio was 1:10 [curve (c)]. Selectivity to the C-5-(*S*) center was greater than 95% in all cases (taking into account conversions). The same phenomena can be observed when THF is used as solvent. The reaction was slower than in dioxane, although the enzyme retained a high regioselectivity (equal to or greater than 95%, relative to conversions) to the C-5 hydroxyl group (entries 7−9, Table 1).

When the study was centered on stereoisomer **3c**, the enzyme showed a high regioselectivity toward the C-5 hydroxyl group in all cases (94−100%, taking into account the formation of compounds **7** and **8**, which are C-5 regioisomers, and conversions). In toluene, a 1:10 (**3c**:**4**) ratio was necessary. If 1:2 or 1:4 ratios were used, carbonate **4** was consumed, and after some time oxime derivative **8** began to appear as a consequence of the formation of dioxime carbonate (entries 1−3, Table 2), which the enzyme then used as an alkoxycarbonylation reagent, thus competing with the original carbonate **4** that had initially been added. This fact is not an inconvenience from the synthetic point of view because

Table 2. Regioselective Enzymatic Alkoxycarbonylation of 3c with 4



entry	solvent	*T* (°C)	ratio[a]	*t* (h)	conv (%)[b]	**7** (%)[c]	**8** (%)[c]	**9** (%)[c]
1	toluene	30	1:10	20	93	83	7	3
2	toluene	30	1:4	17	89	70	16	3
3	toluene	30	1:2	16	76	67	9	
4	1,4-dioxane	60	1:10	258	78	71	3	4
5	1,4-dioxane	60	1:(4+4+2)[d]	166	82	61	17	4
6	THF	30	1:10	189	46	46		
7	THF	60	1:10	96	72	72		
8	THF	30	1:(4+3+3)[d]	99	54	52	2	
9	THF	60	1:(4+6)[d]	89	95	85	4	6

[a] Ratio between **3c** and **4**. [b] Calculated by GC. [c] Percentage of product formation calculated by GC. [d] Added in several portions, as indicated.

both compounds, **7** and **8**, are appropriate synthons for use as precursors to introduce additional functionalities. In contrast, with stereoisomer **3b**, the reaction of **3c** with THF was faster than with 1,4-dioxane (Table 2), although in both solvents the inhibition of the enzyme mentioned above was patent. To obtain an appreciable degree of conversion for both dioxane and THF, a 1:10 ratio was essential, as was the use of more drastic conditions (60 °C). To avoid the inhibition process, subsequent portions of carbonate **4** were added until 10 equiv was reached in the reaction vessel. As shown in Table 2 (entries 4 and 5), this strategy favored the transformation of starting diol **3c**. Even so, reaction times were too long in dioxane. In THF, reaction times decreased considerably, giving rise to a 95% conversion at 60 °C in 89 h using two portions (4 and 6 equiv) of alkoxycarbonylating agent. As shown by GC, a high percentage of regioselectivity was obtained, and these conditions proved especially appropriate for compound **7** (entry 9, Table 2), which has the hydroxyl group in the C-5 position protected.

The facts related to the enzymatic process in THF are brought together in graphical form in Figure 2. In general, all of the reactions were left to run until no more C-5 vinyloxy derivative was formed. It is possible to see clearly that if the process takes place at 30 °C in a ratio 1:10, the formation of C-5 vinyloxy product **7** goes as far as 46% in 189 h but does not progress appreciably [curve (d) and entry 6 in Table 2]. This result shows an important extent of inhibition by carbonate **4**. In more drastic conditions (60 °C, ratio 1:10) [curve (b)] the results get better, with 72% of compound **7** being obtained at 96 h, although no evolution takes place if the reaction runs until 124 h (entry 7, Table 2). Better results can be obtained if the alkoxycarbonylating reagent is added in portions (entries 8 and 9, Table 2), thereby avoiding the inhibition process, at both 30 °C [curve (c)] and 60 °C [curve (a)]. The latter represents the best conditions for the preparation of compound **7** (85% regioselectivity to the C-5 hydroxyl group): shorter reaction time, higher conversion, and better regioselectivity. As can be seen in Table 2, one fact is noteworthy: reactions run in toluene at 30 °C (entry 1, Table 2), as well as in THF at 60 °C (adding **4** in portions, 4 and 6 equiv) (entry 9,

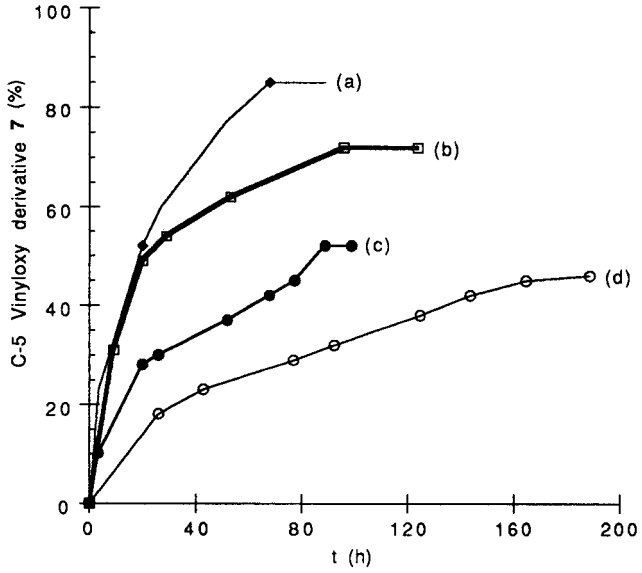
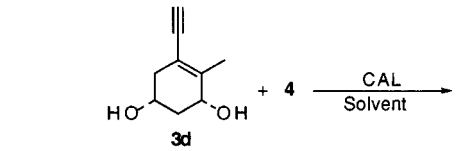


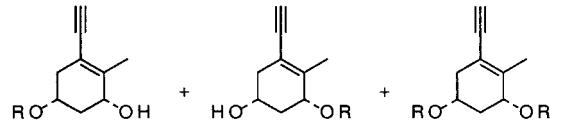
Figure 2. Enzymatic alkoxycarbonylation in THF of diol **3c** with carbonate **4** catalyzed by CAL at different temperatures and ratios between **3c** and **4**: (a) 60 °C, 1:(4 + 6), (b) 60 °C, 1:10, (c) 30 °C, 1:(4 + 3 + 3), and (d) 30 °C, 1:10.

Table 2), constitute the optimal conditions to prepare compound **7**.

Following the study of enzymatic alkoxycarbonylation of all stereoisomers of the A-ring synthon of 1α,25-$(OH)_2$-D_3, we centered our attention in isomer **3d,** which is the enantiomer of **3c**. Taking into account the previous results in enzymatic acylation with CVL, we expected behavior for stereoisomer **3d** different from that of the others (**3a**−**c**). One surprising result was obtained. The enzyme showed the same regioselectivity toward the C-5-(*R*) hydroxyl group, although results were slightly inferior to those for **3a**−**c** in this alkoxycarbonylation process. When the reaction was carried out at 30 °C in toluene with a ratio 1:10 (**3d**:**4**), in 140 h the conversion was 96%. Together with **10**, the C-5 vinyloxy carbonylated product, a considerable amount of dialkoxycarbonylated compound **13** (entry 1, Table 3) appeared. From the second day of reaction, the presence of compound **13** was observed. To avoid this formation, the process was carried out at 60 °C to reduce the reaction time. At the beginning, the formation of C-5 vinyloxy derivative **10** was observed, although this compound evolves toward C-5 oximeoxy derivative **11** (followed by GC analysis) (entry 3, Table 3). In the purification of the reaction crude it was not possible to identify any single product, the result being a complex mixture of unidentified products, nor did the process show any improvement in similar conditions at 45 °C (entry 2, Table 3). To increase the regioselectivity shown by CAL, the reaction was performed in dioxane. In the reaction conditions indicated in entry 4 (Table 3), it was observed that the process took place with a high percentage of regioselectivity, but the conversion was very low as a result of inhibition of CAL by **4**. Thus, in entry 5 (Table 3) we added carbonate **4** in smaller portions to avoid the inhibition process, obtaining results similar to those when toluene was used at 60 °C (entry 3, Table 3) in relation to the ratio between C-5 vinyloxy and C-5 oximeoxy products. However, in this case the regioselectivity toward the C-5-(*R*) hydroxyl group was complete. The change from dioxane to THF did not result in any improvement in the results (entries 6−7, Table

Table 3. Regioselective Enzymatic Alkoxycarbonylation of 3d with 4[a]





10, R= $CO_2CH{=}CH_2$ **12**, R= $CO_2CH{=}CH_2$ **13**, R= $CO_2CH{=}CH_2$
11, R= $CO_2N{=}CMe_2$

entry	solvent/ratio[b]	*T* (°C)	*t* (h)	conv (%)	**10** (%)	**11** (%)	**12** (%)	**13** (%)
1	tol/1:10	30	140	96	64	9	2	21
2	tol/1:10	45	51	76	22	35		19
3	tol/1:10	60	3.5	100	7	77		15
4	diox/1:10[c]	60	96	36	31		2	3
5	diox/1:10[d]	60	79	84	9	75		
6	THF/1:10[c]	60	96	33	30		1	2
7	THF/1:10[d]	60	118	48	33	12		3

[a] All percentages in this table were calculated by GC. [b] Ratio between **3d** and **4**. [c] Added in two portions: 4 + 6. [d] Added in three portions: 4 + 3 + 3.

3). Taking into account these surprising results, an alkoxycarbonylation reaction catalyzed by CVL was carried out. This enzyme did not show the excellent regioselectivity toward C-3 that it had exhibited in the enzymatic acylation process with vinyl esters, a mixture of mono- (C-3 and C-5) and dialkoxycarbonylation products being obtained with poor selectivity. Similar unpromising results were obtained in the enzymatic acylation reaction catalyzed by CAL.

The synthetic utility of carbonates **5**, **7**, and **10** derived from A-ring synthons has been shown through preparation of important carbamates such as **15**−**17**. We chose different amines **14** to obtain several families of carbamates. The simplest one, **15a**−**17a**, was prepared from **5**, **7**, and **10** reacting with ammonia.

Thus, *N*,*N*-unsubstituted carbamates of A-ring synthons were obtained when ammonia was bubbled at 0 °C in THF, and the mixtures were then allowed to react at 30 °C for 22 h. The compounds were obtained essentially pure by ^{1}H NMR, in quantitative yields and without the need for further purification. The second objective was to introduce an additional amino group at the R moiety of **15**−**17** at different distances from the carbamate group. The closest is when an amino group is on the nitrogen of the carbamate, giving rise to carbazate A-ring synthons. Although this is a rare functional group, it has shown important activities[14] and has been used to prepare nucleoside[8a] and dinucleotide derivatives.[8b] To shorten reaction times, 5 equiv of hydrazine was added. The process took place in 3.5 h at room temperature, giving A-ring derivatives **15b**−**17b** with excellent yields and without the need of a purification step. Interesting products to synthesize are A-ring carbamates that possess an amino group at the end of an alkyl chain. Thus, 1,3-diaminopropane was reacted at 60 °C with the C-5

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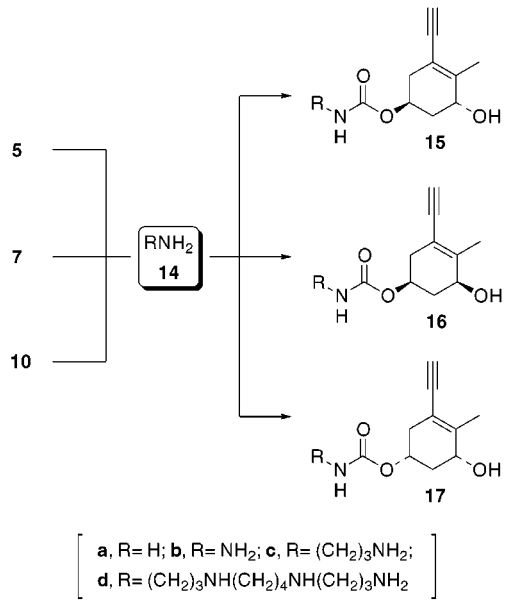
Scheme 1



vinyl carbonates of A-ring isomers **5**, **7**, and **10** to obtain *N*-(aminoalkyl)carbamates **15c**−**17c** with excellent yields. It is noteworthy that only monocarbamates were formed. Given the importance of polyamino carbamates we extended the aforementioned methodology to synthesized A-ring precursors **15d**−**17d**. The spermine **14d**, a linear tetra-amine, was chosen because of its occurrence in all cells and its important role in vivo.[9] Spermine reacted with carbonate **7** at 60 °C, giving rise in 9 h to monopolyaminocarbamate **15d** as a major product and, as a minor product (∼10% yield), compound **18**, whose structure corresponds to the addition of two A-ring fragments at both ends of the spermine skeleton. To avoid the formation of the latter derivative, we used a reaction temperature of 40 °C instead of 60 °C, and in 18 h the starting carbonate **7** completely disappeared. In these conditions, formation of **18** was minimized to traces and monopolyaminocarbamates **15d**−**17d** were obtained in high yield (70−75%).

The structural assignment of the compounds described in this paper is based on the analysis of their ^{1}H and ^{13}C NMR spectra and DEPT experiments. The correct assignments were confirmed by ^{1}H−^{1}H homonuclear and ^{1}H−^{13}C heteronuclear correlation experiments. The full assignment of the ^{1}H and ^{13}C NMR spectra is given in the Experimental Section.

Summary

C. antarctica lipase (CAL) has already demonstrated its behavior in the enzymatic alkoxycarbonylation process with 1α,25-dihydroxyvitamin D_3 A-ring synthon **3a**. Regioselective transformation occurred only at the C-5-(*R*) hydroxyl group. The stereoisomers of A-ring synthon **3a**, named **3b**−**3d**, were subjected to a very comprehensive regioselective enzymatic study with CAL. From this, it emerged that the enantiomer of natural A-ring synthon **3b** was a very good substrate for CAL in toluene, dioxane, or THF, showing in all cases conversions close to 100% and regioselectivities equal to or greater than 95% toward the C-5-(*S*) hydroxyl group. Inhibition by carbonate **4** was evident when its ratio was increased from 1:2 to 1:10. Stereoisomer **3c** carried out the regioselective enzymatic transformation best in toluene at 30 °C or in THF at 60 °C. The regioselectivity showed a preference toward the C-5-(*S*) hydroxyl group. The 1:10 ratio (diol:carbonate) was mandatory to obtain an acceptable degree of conversion (in dioxane or THF). To avoid inhibition processes, subsequent portions of carbonate **4** were added. A-ring synthon **3d** has a surprising conduct because it suffers C-5-(*R*) enzymatic alkoxycarbonylation, while in acylation processes with CVL it showed the behavior opposite to that observed for **3a**−**3c**, which was C-3-(*R*) regioselective acylation. Additionally, an efficient chemoenzymatic synthesis of A-ring synthon carbamate derivatives **15a,c**−**17a,c**, including carbazates **15b**−**17b**, and polyamino carbamates **15d**−**17d** was accomplished by a two-step strategy, involving the regioselective enzymatic synthesis of carbonates **5**, **7**, and **10**, followed by reaction with (poly)amino derivatives **14**. The procedure provides a convenient synthesis of carbamates **15a,c**−**17a,c**, carbazates **15b**−**17b**, and polyamino carbamates **15d**−**17d** derived from A-ring precursors **3** under mild reaction conditions.

Experimental Section[15]

General. *C. antarctica* lipase, CAL SP 435L, was a gift from Novo Nordisk Co. All other reagents were purchased from Aldrich or Fluka. Solvents were distilled over an adequate desiccant under nitrogen. Gas chromatography was carried out with flame ionization detection (FID) and a 25 m HP-1 capillary column coated with methylsilicone gum using nitrogen as carrier gas. The method used was injector and detector temperatures set at 280 °C; column initial temperature 150 °C (3 min), rate 18 °C/min, column final temperature 260 °C (5 min). With this method, compound **3b** appeared at 4.86 min, **3c** and **3d** at 4.83 min, **5** at 7.19 min, **6** at 7.02 min, **7** and **10** at 6.88 min, **8** and **11** at 7.69 min, **9** and **13** at 8.74 min, and **12** at 6.90 min. Compounds **3b**−**3d** were previously described by Okamura and co-workers.[11,12h]

Enzymatic Alkoxycarbonylation of Diol 3b with Acetone *O*-[(Vinyloxy)carbonyl]oxime (4). Synthesis of (3*R*,5*S*)-1-Ethynyl-3-hydroxy-2-methyl-5-[(vinyloxy)carbonyloxy]-1-cyclohexene (5). To a solution of **3b** (20 mg, 0.132 mmol) in 5 mL of solvent (THF, 1,4-dioxane, or toluene) was added 90 mg of CAL and carbonate **4** [1.320 (1:10), 0.528 (1:4), or 0.264 (1:2) mmol]. The suspension was shaken at 30 °C, and the progress of the reaction was followed by TLC and GC analysis until no further reaction was apparent. After removal of the enzyme by filtration, evaporation of the solvent, and ^{1}H NMR analysis, the residual mixture was purified by flash chromatography (silica gel, with gradient eluent 15−40% ethyl acetate/hexanes) to give C-5 monovinyloxycarbonylation derivative **5** as a major product (or unique, yields ranged from 84% to 93%), and C-3 vinyloxycarbonylation compound **6** as a minor product, depending on conditions. All of these data are summarized in Table 1. Data for **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 and 1.89 (br s, 1H, OH), 2.02 (s, 3H, H_9), 1.85−2.21 (m, 2H, H_4), 2.32 (dd, 1H, H_{6ax}, $^2J_{HH}$ = 17.0, $^3J_{HH}$ = 7.3 Hz), 2.68 (dd, 1H, H_{6eq}, $^2J_{HH}$ = 17.4, $^3J_{HH}$ = 3.9 Hz), 3.11 (s, 1H, H_8), 4.30 (br s, 1H, H_3), 4.58 (dd, 1H, H_{12}-cis, $^3J_{HH}$ = 6.3, $^2J_{HH}$ = 1.9 Hz), 4.92 (dd, 1H, H_{12}-trans, $^3J_{HH}$ = 13.6, $^2J_{HH}$ = 1.9 Hz), 5.08 (m, 1H, H_5), and 7.07 (dd, 1H, H_{11}, $^3J_{HH}$ = 13.6, $^3J_{HH}$ = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.3 (C_9), 34.7 (C_6), 36.0 (C_4), 68.1 (C_3), 71.3 (C_5), 80.9 (C_8), 82.4 (C_7), 97.9 (C_{12}), 113.6 (C_1), 142.4 (C_{11}), 142.8 (C_2), and 152.0 (C_{10}).

(15) For all products, full spectral data are given in the Supporting Information. Selected ^{1}H and ^{13}C NMR signals for major products and data for minor compound **18** are also presented in the Experimental Section. The purity of all major and minor derivatives was estimated by a combination of GC and NMR analysis. The level of purity is indicated by the inclusion of copies of ^{1}H and ^{13}C NMR spectra in the Supporting Information.

Enzymatic Alkoxycarbonylation of Diol 3c with Acetone *O*-[(Vinyloxy)carbonyl]oxime (4). Synthesis of (3*S*,5*S*)-1-Ethynyl-3-hydroxy-2-methyl-5-[(vinyloxy)carbonyloxy]-1-cyclohexene (7). The procedure as described for **3b** gave, after flash chromatography (silica gel, with gradient eluent 15−50% EtOAc/hexane), C-5 monovinyloxycarbonylation product **7** (major or unique product, yields ranged from 87% to 97%), C-5 oximecarbonate **8**, and C-3,5 divinyloxycarbonylation product **9,** depending on conditions. All of these data are summarized in Table 2. Data for **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (br s, 1H, OH), 2.06 (s, 3H, H_9), 2.09 (ddd, 1H, H_{4eq}, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 5.7, $^3J_{HH}$ = 2.4 Hz), 2.22 (ddd, 1H, H_{4ax}, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 6.5, $^3J_{HH}$ = 4.2 Hz), 2.52 (m, 2H, H_6), 3.12 (s, 1H, H_8), 4.11 (br s, 1H, H_3), 4.59 (dd, 1H, H_{12}-cis, $^3J_{HH}$ = 6.1, $^2J_{HH}$ = 2.0 Hz), 4.91 (dd, 1H, H_{12}-trans, $^3J_{HH}$ = 13.8, $^2J_{HH}$ = 2.0 Hz), 5.11 (m, 1H, H_5), and 7.06 (dd, 1H, H_{11}, $^3J_{HH}$ = 13.8, $^3J_{HH}$ = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.6 (C_9), 34.4 (C_6), 34.8 (C_4), 67.2 (C_3), 72.1 (C_5), 81.1 (C_8), 82.5 (C_7), 98.1 (C_{12}), 112.1 (C_1), 142.3 (C_{11}), 143.5 (C_2), and 151.5 (C_{10}).

(3*S*,5*S*)-1-Ethynyl-3-hydroxy-2-methyl-5-[(acetonoxime)carbonyloxy]-1-cyclohexene (8): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.98 (s, 3H, H_{12}), 1.99 (s, 3H, H_{12}), 1.97−2.10 (m, 1H, H_4), 2.05 (br s, 3H, H_9), 2.24 (dddd, 1H, H_4, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 5.9, $^3J_{HH}$ = 3.6, $^4J_{HH}$ = 1.0 Hz), 2.41−2.67 (m, 2H, H_6), 2.70 (br s, 1H, OH), 3.11 (s, 1H, H_8), 4.06 (m, 1H, H_3), and 5.20 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.8 (C_{12}), 18.8 (C_9), 21.7 (C_{12}), 34.3 and 34.5 (C_4 and C_6), 67.0 (C_3), 72.0 (C_5), 80.9 (C_8), 82.7 (C_7), 111.8 (C_1), 143.6 (C_2), 152.7 (C_{10}), and 163.5 (C_{11}).

Enzymatic Alkoxycarbonylation of Diol 3d with Acetone *O*-[(Vinyloxy)carbonyl]oxime (4). Synthesis of (3*R*,5*R*)-1-Ethynyl-3-hydroxy-2-methyl-5-[(vinyloxy)carbonyloxy]-1-cyclohexene (10). The procedure as described for **3c** gave C-5 monovinyloxycarbonylation product **10** and/or C-5 oximecarbonate **11** and/or C-3 monovinyloxycarbonylation product **12** and/or C-3,5 divinyloxycarbonylation product **13,** depending on conditions. All of these data are summarized in Table 3. Data for **10**: same as for its enantiomer, compound **7**.

(3*R*,5*R*)-1-Ethynyl-3-hydroxy-2-methyl-5-[(acetonoxime)carbonyloxy]-1-cyclohexene (11): same data as for its enantiomer, compound **8**.

(3*R*,5*R*)-1-Ethynyl-2-methyl-3,5-bis[(vinyloxy)carbonyloxy]-1-cyclohexene (13): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.97 (s, 3H, H_9), 2.29 (m, 2H, H_4), 2.56 (m, 2H, H_6), 3.19 (s, 1H, H_8), 4.59 (dd, 1H, H_{12}-cis or H_{15}-cis, $^3J_{HH}$ = 6.2, $^2J_{HH}$ = 2.1 Hz), 4.60 (dd, 1H, H_{12}-cis or H_{15}-cis, $^3J_{HH}$ = 6.2, $^2J_{HH}$ = 1.8 Hz), 4.92 (dd, 1H, H_{12}-trans or H_{15}-trans, $^3J_{HH}$ = 13.9, $^2J_{HH}$ = 2.1 Hz), 4.94 (dd, 1H, H_{12}-trans or H_{15}-trans, $^3J_{HH}$ = 13.9, $^2J_{HH}$ = 2.1 Hz), 4.97 (m, 1H, H_5), 5.34 (t, 1H, H_3, $^3J_{HH}$ = 6.0 Hz), 7.06 and 7.08 (2dd, 2H, H_{11} and H_{14}, $^3J_{HH}$ = 13.9, $^3J_{HH}$ = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.9 (C_9), 32.1 (C_4), 34.5 (C_6), 70.2 (C_5), 73.8 (C_3), 81.8 (C_7), 82.3 (C_8), 98.1 (C_{12} and C_{15}), 115.8 (C_1), 138.4 (C_2), 142.4 and 142.5 (C_{11} and C_{14}), 151.9 and 152.4 (C_{10} and C_{13}).

Ammonolysis Reaction of Carbonates 5, 7, and 10. Synthesis of A-Ring Carbamate Derivatives 15a−17a. To a solution of carbonate **5** (or **7** or **10**) (20 mg, 0.091 mmol) in THF (15 mL) was bubbled ammonia during 30 min at 0 °C. The solution was stirred at 30 °C until no starting material remained (approximately 22 h). Then, solvent was evaporated under reduced pressure. The residue was substantially pure without purification steps (yields ranged from 95% to 98%).

(3*R*,5*S*)-5-(Carbamoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (15a): ^{1}H NMR (MeOH-d_4, 400 MHz) δ 2.13 (m, 2H, H_4), 2.17 (s, 3H, H_9), 2.35 (dd, 1H, H_6, $^2J_{HH}$ = 17.0, $^3J_{HH}$ = 6.5 Hz), 2.75 (d, 1H, H_6, $^2J_{HH}$ = 17.0 Hz), 3.67 (s, 1H, H_8), 4.39 (t, 1H, H_3, $^3J_{HH}$ = 4.7 Hz), and 5.16 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 100.6 MHz) δ 18.9 (C_9), 36.8 (C_6), 37.9 (C_4), 68.5 (C_5), 69.0 (C_3), 82.3 (C_8), 84.2 (C_7), 115.3 (C_1), 144.5 (C_2), and 159.7 (C_{10}).

(3*S*,5*S*)-5-(Carbamoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (16a): ^{1}H NMR (MeOH-d_4, 200 MHz) δ 1.95 (ddd, 1H, H_4, $^2J_{HH}$ = 12.7, $^3J_{HH}$ = 9.7, $^3J_{HH}$ = 7.5 Hz), 2.16 (s, 3H, H_9), 2.43 (m, 2H, H_{4eq} + H_{6ax}), 2.66 (m, 1H, H_{6eq}), 3.68 (s, 1H, H_8), 4.37 (apparent t, 1H, H_3, $^3J_{HH}$ = 6.5 Hz), and 4.97 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 50.3 MHz) δ 18.3 (C_9), 37.0 (C_6), 38.4 (C_4), 68.9 (C_5), 69.4 (C_3), 82.4 (C_8), 84.1 (C_7), 114.4 (C_1), 145.5 (C_2), and 159.5 (C_{10}).

(3*R*,5*R*)-5-(Carbamoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (17a): same data as for its enantiomer, compound **16a**.

Hydrazinolysis Reaction of Carbonates 5, 7, and 10. Synthesis of A-Ring Carbazate Derivatives 15b−17b. To a solution of carbonate **5** (or **7** or **10**) (20 mg, 0.091 mmol) in THF (0.5 mL) was added hydrazine (14.2 μL, 0.453 mmol). The solution was stirred under nitrogen atmosphere at room temperature until no starting material remained (3.5 h). Then, solvent was evaporated under reduced pressure. The residue was substantially pure without purification steps (yields ranged from 94% to 97%).

(3*R*,5*S*)-5-(Carbazoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (15b): ^{1}H NMR (MeOH-d_4, 200 MHz) δ 2.14 (m, 2H, H_4), 2.17 (s, 3H, H_9), 2.36 (dd, 1H, H_{6ax}, $^2J_{HH}$ = 17.2, $^3J_{HH}$ = 5.7 Hz), 2.77 (ddd, 1H, H_{6eq}, $^2J_{HH}$ = 17.2, $^3J_{HH}$ = 3.2, $^4J_{HH}$ = 1.6 Hz), 3.67 (s, 1H, H_8), 4.38 (apparent t, 1H, H_3, $^3J_{HH}$ = 5.0 Hz), and 5.22 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 75.5 MHz) δ 18.9 (C_9), 36.8 (C_6), 37.9 (C_4), 68.9 (C_3), 69.2 (C_5), 82.3 (C_8), 84.1 (C_7), 115.1 (C_1), 144.5 (C_2), and 160.4 (C_{10}).

(3*S*,5*S*)-5-(Carbazoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (16b): ^{1}H NMR (MeOH-d_4, 400 MHz) δ 1.98 (m, 2H, H_{4ax}), 2.17 (s, 3H, H_9), 2.37−2.53 (m, 2H, H_{4eq} + H_{6ax}), 2.67 (d, 1H, H_{6eq}, $^2J_{HH}$ = 17.0 Hz), 3.67 (s, 1H, H_8), 4.37 (apparent t, 1H, H_3, $^3J_{HH}$ = 6.4 Hz), and 5.08 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 75.5 MHz) δ 18.3 (C_9), 37.0 (C_6), 38.4 (C_4), 69.3 (C_3), 69.5 (C_5), 82.4 (C_8), 84.1 (C_7), 114.4 (C_1), 145.5 (C_2), and 160.3 (C_{10}).

(3*R*,5*R*)-5-(Carbazoyloxy)-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (17b): same data as for its enantiomer, compound **16b**.

Aminolysis Reaction of Carbonates 5, 7, and 10 with Propan-1,3-diamine (14c). Synthesis of A-Ring *N*-(aminoalkyl)carbamate Derivatives 15c−17c. To a solution of carbonate **5** (or **7** or **10**) (20 mg, 0.091 mmol) in THF (5 mL) was added propan-1,3-diamine (18.9 μL, 0.227 mmol). The solution was stirred under nitrogen atmosphere at 60 °C until no starting material remained (28 h). Then, solvent was evaporated under reduced pressure, and the residue was subjected to flash chromatography (silica gel, 1% NH_3(aq)/MeOH) (yields ranged from 93% to 95%).

(3*R*,5*S*)-5-[[*N*-(3-Aminopropyl)carbamoyl]oxy]-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (15c): ^{1}H NMR (MeOH-d_4, 400 MHz) δ 1.85 (p, 2H, H_{12}, $^3J_{HH}$ = 7.0 Hz), 2.12 (m, 2H, H_4), 2.17 (s, 3H, H_9), 2.34 (dd, 1H, H_{6ax}, $^2J_{HH}$ = 17.1, $^3J_{HH}$ = 6.0 Hz), 2.75 (d, 1H, H_{6eq}, $^2J_{HH}$ = 17.1 Hz), 2.89 (t, 2H, H_{13}, $^3J_{HH}$ = 7.0 Hz), 3.35 (t, 2H, H_{11}, $^3J_{HH}$ = 6.6 Hz), 3.66 (s, 1H, H_8), 4.38 (m, 1H, H_3), and 5.18 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 100.6 MHz) δ 18.9 (C_9), 33.5 (C_{12}), 36.9 (C_6), 38.0 (C_4), 39.2 (C_{11}), 39.8 (C_{13}), 68.7 (C_5), 69.0 (C_3), 82.2 (C_8), 84.2 (C_7), 115.2 (C_1), 144.6 (C_2), and 159.0 (C_{10}).

(3*S*,5*S*)-5-[[*N*-(3-Aminopropyl)carbamoyl]oxy]-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (16c): ^{1}H NMR (MeOH-d_4, 200 MHz) δ 1.85 (p, 2H, H_{12}, $^3J_{HH}$ = 6.8 Hz), 1.95 (m, 1H, H_{4ax}), 2.16 (s, 3H, H_9), 2.41 (m, 1H, H_{4eq}), 2.46 (m, 1H, H_{6ax}), 2.65 (m, 1H, H_{6eq}), 2.89 (t, 2H, H_{11}, $^3J_{HH}$ = 6.7 Hz), 3.36 (t, 2H, H_{13}, $^3J_{HH}$ = 6.7 Hz), 3.69 (s, 1H, H_8), 4.37 (apparent t, 1H, H_3, $^3J_{HH}$ = 6.0 Hz), and 4.99 (m, 1H, H_5); ^{13}C NMR (MeOH-d_4, 100.6 MHz) δ 18.3 (C_9), 33.4 (C_{12}), 37.1 (C_6), 38.5 (C_4), 39.1 (C_{11}), 39.7 (C_{13}), 69.1 (C_5), 69.4 (C_3), 82.4 (C_8), 84.1 (C_7), 114.4 (C_1), 145.5 (C_2), and 158.8 (C_{10}).

(3*R*,5*R*)-5-[[*N*-(3-Aminopropyl)carbamoyl]oxy]-1-ethynyl-3-hydroxy-2-methyl-1-cyclohexene (17c): same data as for its enantiomer, compound **16c**.

Aminolysis Reaction of Carbonates 5, 7, and 10 with Spermine (14d). Synthesis of A-Ring Polyamino Carbamate Derivatives 15d−17d. To a solution of carbonate **5** (or **7** or **10**) (20 mg, 0.091 mmol) in THF (5 mL) was added spermine (45.9 mg, 0.227 mmol). The solution was stirred under nitrogen atmosphere at 40 °C until no starting material

remained (18 h). Then, solvent was evaporated under reduced pressure, and the residue was subjected to flash chromatography (silica gel, 1:2:2 NH_3(aq)/MeOH/CH_2Cl_2) to give C-5 monospermine derivative (yields ranged from 70% to 75%).

(3*R*,5*S*)-1-Ethynyl-3-hydroxy-2-methyl-5-[[*N*^{1}-(spermine)carbamoyl]oxy]-1-cyclohexene (15d): ^{1}H NMR (40 °C, MeOH-d_4, 200 MHz) δ 1.69−2.02 (m, 8H, $2H_{12} + 2H_{15} + 2H_{16} + 2H_{19}$), 2.12 (m, 2H, H_4), 2.17 (s, 3H, H_9), 2.33 (dd, 1H, H_6, $^2J_{HH} = 17.2$, $^3J_{HH} = 6.7$ Hz), 2.66−3.12 (m, 11H, $1H_6 + 2H_{13} + 2H_{14} + 2H_{17} + 2H_{18}+2H_{20}$), 3.35 (t, 2H, H_{11}, $^3J_{HH} = 6.6$ Hz), 3.68 (s, 1H, H_8), 4.38 (apparent t, 1H, H_3, $^3J_{HH} = 5.1$ Hz), and 5.17 (m, 1H, H_5); ^{13}C NMR (40 °C, MeOH-d_4, 50.3 MHz) δ 18.9, 28.1, 30.5, 31.7, 37.0, 38.0, 39.6, 40.6, 47.7, 48.2, 50.3, 68.7, 69.0, 82.3, 84.2, 115.2, 144.6, and 158.9.

(3*S*,5*S*)-1-Ethynyl-3-hydroxy-2-methyl-5-[[*N*^{1}-(spermine)carbamoyl]oxy]-1-cyclohexene (16d): ^{1}H NMR (MeOH-d_4, 200 MHz) δ 1.96 (m, 1H, H_4), 2.03−2.55 (series of m, 10H, $2H_{12} + 2H_{15} + 2H_{16} + 2H_{19} + 1H_4 + 1H_6$), 2.17 (s, 3H, H_9), 2.66 (m, 1H, H_6), 3.25 (m, 10H, $2H_{13} + 2H_{14} + 2H_{17} + 2H_{18} + 2H_{20}$), 3.43 (t, 2H, H_{11}, $^3J_{HH} = 6.7$ Hz), 3.70 (s, 1H, H_8), 4.38 (m, 1H, H_3), and 5.00 (m, 1H, H_5); ^{13}C NMR (40 °C, MeOH-d_4, 75.5 MHz) δ 18.3, 23.9, 24.1, 25.7, 27.9, 37.1, 38.3, 38.5, 39.0, 46.3, 47.1, 48.1, 48.2, 69.4, 69.5, 82.4, 84.2, 114.4, 145.7, and 158.8.

(3*R*,5*R*)-1-Ethynyl-3-hydroxy-2-methyl-5-[[*N*^{1}-(spermine)carbamoyl]oxy]-1-cyclohexene (17d): same data as for its enantiomer, compound **16d**.

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Supporting Information Available: Complete ^{1}H and ^{13}C NMR spectral data in addition of mp, IR, microanalysis, and MS (and/or HRMS) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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