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Consecutive and Domino Processes for the Synthesis of a Heavily Functionalised Tricyclic System.

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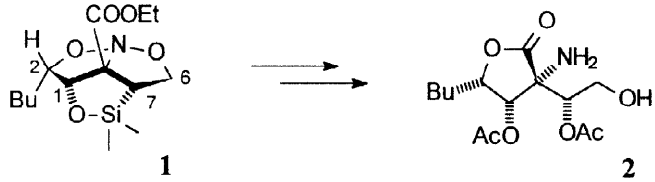
Abstract: One pot multi-bond forming reactions are one of the ways to address the ever growing demand for efficiency in organic synthesis that concern the chemical community. This paper presents a new three-component domino process that efficiently combines four bond-forming reaction steps into a single synthetic operation. From easily available linear starting materials and under very mild conditions, this process builds five new bonds and four new chiral centers, giving rise to the selective formation of a new class of fused heteroatomic tricyclic system, which may be exploited for the synthesis of biologically interesting aminopolyhydroxylated compounds.

The synthesis of complex molecules is traditionally performed by a chain of separate reaction steps, each step requiring its own conditions, reagents, solvent, and catalyst. After each reaction is complete the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Now environmental and economical pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations.[1] These new issues can be addressed by the development of new synthetic methods that, bringing together small and simple components, generate highly complex structures in one pot, much the same way as Nature does. Though the origins of this type of processes can be dated back to the Robinson-Schöpf synthesis of tropinone,[2] it was only recently that terms like *multicomponent reactions*[3] and *domino reactions*[4] became familiar.

These considerations are driving our efforts[5] in developing new methodologies for the preparation of amino polyols, a biologically relevant class of compounds with enzyme-inhibition properties. Recent reports[6] from this laboratory have disclosed that new and heavily functionalised tricyclic compounds, such as **1**, can be easily unfolded into polyhydroxylated amino acid derivatives **2** (Eq. 1).



1 **2** (1)

We wish to report here that the complex tricyclic compounds of type **1** can be obtained in a single, one-pot, three-component reaction from easily and commercially available starting materials under very mild conditions. (Scheme 1).

The reaction is simply performed by bringing together, at room temperature, an aldehyde bearing a leaving group on the α-carbon, an activated primary nitroalkane, and chlorodimethylvinylsilane in the presence of imidazole as the base and in dichloromethane as the solvent. The process involves four bond-forming events that occur spontaneously one after the other: a nitroaldol (Henry) reaction,[7] a ring-closure,[8] a vinylsilicon derivatization[9] of the newly formed hydroxyl group, and an intramolecular 1,3–dipolar cycloaddition.

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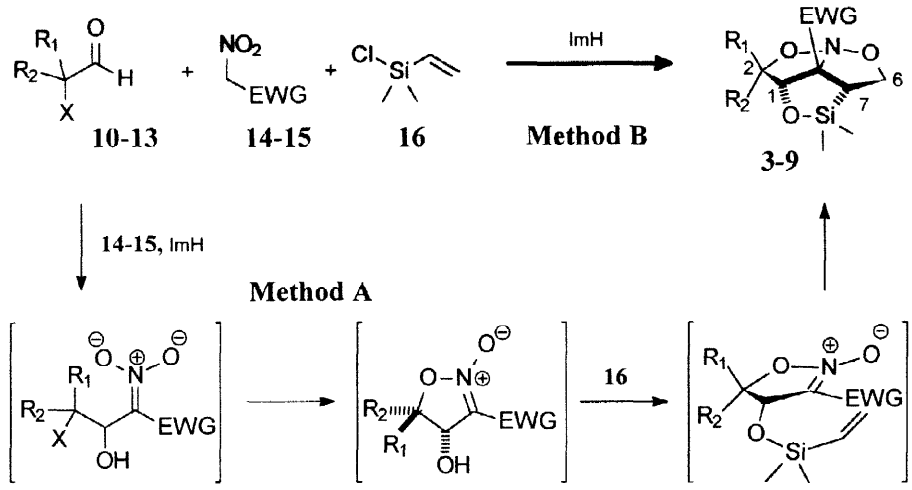

Scheme 1

The synthesis of tricyclic compounds **3-9** were performed both by one-pot consecutive sequences (method A) and by domino sequences (method B) (Scheme 1). In method A chlorodimethylvinylsilane (**16**) was added to the reaction mixture after the disappearance of the starting materials (aldehydes **10-13** and nitroalkanes **14-15**) was observed by TLC, while in a domino process all the reagents were put in the reaction flask from the beginning. Table 1 summarizes the results obtained.

Table 1. One-pot consecutive and domino preparation of tricyclic compounds **3-9**.

					Consecutive		**Domino**	
Aldehyde, Nitroalkane, and Product	R^1	R^2	X	EWG	Isolated Yield (%)	cis/trans ratio	Isolated Yield (%)	cis/trans ratio
10, 14, 3:	H	*n*-$C_{12}H_{25}$	Br	COOEt	83	1.63	61	1.00
10, 15, 4:	H	*n*-$C_{12}H_{25}$	Br	SO_2Ph	84	0.04	57	1.00
11, 14, 5:	H	CH_3	OTs	COOEt	86	1.17	60	1.12
11, 15, 6:	H	CH_3	OTs	SO_2Ph	90	0.56	76	0.66
12, 14, 7:	Ph	CH_3	Br	COOEt	86	0.00	72	0.00
13, 14, 8:	H	$PhCH_2CH_2$	OTs	COOEt	81	0.97	89	1.32
13, 15, 9:	H	$PhCH_2CH_2$	OTs	SO_2Ph	86	0.45	87	0.88

It should be noted that the tricyclization reactions carried out according both to the one-pot consecutive sequence and to domino conditions gave the products in more than satisfactory yields, especially considering that these are the isolated overall yields of four different sequential reactions. The overall process is completely chemo- and regiospecific, and is rather stereoselective since the tricyclic products are obtained as a mixture of only two diastereoisomers (1,2–*trans* and 1,2–*cis*) out of the possible eight (sixteen, considering also the stereogenic nitrogen).

The easy availability of the starting materials allows these reactions to be usually carried out in the multigram scale. In fact the nitroalkanes **14** and **15**, and vinylsilane **16** are all commercially available materials, while the starting α-bromo aldehydes and α–tosyloxy aldehydes (**10-13**)[10] were prepared in one or two steps from commercially available materials even in the enantiomeric pure form. In particular α-bromo aldehydes were obtained by bromination of the corresponding aldehydes and α–tosyloxy aldehydes were obtained by tosylation followed by reduction of the commercially available corresponding enantiomerically pure α–hydroxy esters: methyl (2*S*)-lactate for **11**, and ethyl (2*R*)-4-phenyl-2-hydroxybutanoate for **13**.

The substantial increase in structural complexity on going from the reactants to the products (ΔC_T = +170)[11] illustrates very nicely the great synthetic efficiency of such reaction sequences : starting from acyclic substrate with only one chiral center, easily available enantiomerically pure, they involve the formation of five contiguous chiral centers, four carbons and one nitrogen; the regio- and stereoselective building of three condensed five-membered rings assembled through the formation of five new bonds: two C–C bonds, two C–O bonds and one O–Si bond, all occurring with good yields with a minimum of trouble in what concerns work-up, separation and purification.

The efficiency of the procedures here depicted and the demonstrated conversion of these tricyclic systems to interesting polyhydroxylated aminoacid derivatives,[6] are good arguments that let hope well in useful utilization of them in synthesis of complex structures.

Experimental Section

Method A. Consecutive Conditions. A reaction flask, equipped with a calcium chloride tube, is charged with a mixture of the starting aldehyde (**10-13**, 2.6 mmol), imidazole (2.6 mmol), and the nitroalkane (**14-15**, 2.6 mmol) in dichloromethane (20 cm^3). This mixture is stirred at room temperature (ca. 25 °C) until the consumption of the starting materials is observed by TLC (1 - 6 h). At this point imidazole (6.24 mmol, 2.4 eq) and chlorodimethylvinylsilane (3.12 mmol, 1.2 eq) are added and the mixture is kept stirring until reaction is complete (3 - 12 h). After standard work-up the crude product is purified by flash chromatography.

Method B. Domino Conditions. A reaction flask equipped with a calcium chloride tube is charged with a solution of the starting aldehyde (**10-13**, 2.6 mmol), imidazole (11.7 mmol, 4.5 eq), the nitroalkane (**14-15**, 3.25 mmol, 1.25 eq), and chlorodimethylvinylsilane (3.9 mmol, 1.5 eq) in dichloromethane (20 cm^3). The mixture is stirred at room temperature (ca. 25 °C) and the course of the reaction is monitored by TLC until completion (3 - 12 h). Standard work-up affords the crude product that is purified by flash chromatography.

Physical and spectroscopic data for compounds **3-9**.[12]

cis–**3**: ^{1}H NMR δ 4.75 (*d*, 1, *J* = 3.4), 4.47 (*dd*, 1, *J* = 8.0, 10.0), 4.38 (*dd*,1, *J* = 8.0, 11.1), 4.27 (*dq*, 2, J_d = 1.7, J_q = 7.1), 3.86 (*dt*, 1, J_d = 3.4, J_t = 6.7), 2.43 (*dd*, 1, *J* = 11.1, 10.1), 1.70-1.58 (*m*, 2), 1.35 (*t*, 3, J = 7.1), 1.45-1.20 (*m*, 20), 0.90 (t, 3), 0.37 (*s*, 3), 0.33 (*s*, 3). ^{13}C NMR δ 170.84, 95.91, 86.36, 79.05, 74.53, 62.75, 35.80, 32.38-23.14, 14.57, 14.53, 0.22, -2.64.

trans–**3**: ^{1}H NMR δ 4.78 (*d*, 1, *J* = 3.4), 4.44- 4.20 (*m*, 4), 4.12-4.02 (*m*, 1), 2.55 (*dd*, 1, *J* = 10.1, 10.1), 1.90-1.20 (*m*, 25), 0.88 (*t*, 3), 0.38 (*s*, 3), 0.32 (*s*, 3). ^{13}C NMR δ 170.71, 93.48, 90.06, 86.92, 72.68, 62.64, 36.79, 32.21-22.98, 14.41, 0.28, -2.14.

cis–**4** and *trans*–**4**: ^{1}H NMR δ 8.03 (*m*, 2), 7.63 (*m*, 3), 5.05 (*d*, 0.5, *J* = 3.3, *cis*), 4.98 (*d*, 0.5, *J* = 4.3, *trans*), 4.40-4.20 (*m*, 1.5, *cis* and *trans*), 4.12 (*m*, 1, *trans*), 3.45 (*m*, 0.5), 2.51 (*m*, 1), 1.57 (*m*, 2, *cis*), 1.4-1.11 (*m*, 22), 0.90 (*m*, 3), 0.48 (*s*, 3), 0.36 (*s*, 3). ^{13}C NMR δ 135.11, 131.33, 129.40, 109.77 (cis), 107.53 (trans), 88.17 (trans), 87.60 (trans), 83.50 (cis), 79.60 (cis), 74.91 (cis), 71.19 (trans), 34.83 (trans), 34.35 (cis), 32.39-23.18, 14.61, 0.47, -1.56 (trans), 0.11, -2.64 (cis).

cis–**5**: mp 90-91°C. $[\alpha]_D^{32}$ –37.2 (*c* 0.952, $CHCl_3$). ^{1}H NMR δ 4.74 (*d*, 1, *J* = 3.4), 4.48 (*dd*, 1, *J* = 8.0, 10.0), 4.39 (*dd*, 1, *J* = 8.0, 11.1), 4.28 (*dq*, 2, *J* = 1.9, 7.1), 4.05 (*dq*, 1, *J* = 3.45, 7.1), 2.45 (*dd*, 1, *J* = 11.1, 10.0), 1.34 (*t*, 3, *J* = 7.1), 1.23 (*d*, 3, *J* = 6.3), 0.38 (*s*, 3), 0.33 (*s*, 3). ^{13}C NMR δ 170.2, 95.63, 86.57, 74.41, 74.02, 62.34, 35.32, 14.08, 11.28, -0.26, -3.13.

trans–**5**: $[\alpha]_D^{32}$ +1.56 (*c* 0.920, $CHCl_3$). ^{1}H NMR δ 4.76 (*d*, 1, *J* = 3.5), 4.45-4.20 (*m*, 5), 2.48 (*dd*, 1, *J* = 10.0), 1.35 (*d*, 3, *J* = 6.3), 1.30 (*t*, 3, *J* = 7.1), 0.40 (*s*, 3), 0.33 (*s*, 3). ^{13}C NMR δ 170.77, 93.47, 91.17, 83.09, 72.86, 62.75, 36.83, 17.69, 14.41, -0.36, -2.04.

cis–**6**: mp 97-98°C. $[\alpha]_D^{31}$ -64.4 (*c* 0.95, $CHCl_3$). ^{1}H NMR δ 8.05 (*m*, 2), 7.70 (*m*, 1), 7.60 (*m*, 2), 4.98 (*d*, 1, *J* = 3.5), 4.35 (*dd*, 1, *J* = 8.0, 11.3), 4.31 (*dd*, 1, *J* = 8.1, 10.5), 3.63 (*dq*, 1, J_d = 3.5, J_q = 6.3), 2.50 (*dd*, 1, *J* = 11.0, 10.5), 1.17 (*d*, 3, *J* = 6.3), 0.48 (*s*, 3), 0.37 (*s*, 3). ^{13}C NMR δ 134.72, 130.84, 128.97, 109.50, 83.72, 75.01, 74.44, 33.86, 11.27, -0.35, -2.92.

trans–**6**: mp 106-108°C. $[\alpha]_D^{31}$ +6.41 (*c* 0.99, $CHCl_3$). ^{1}H NMR δ 8.05 (*m*, 2), 7.65 (*m*, 3), 4.95 (*d*, 1, *J* = 4.4), 4.29 (*dq*, 1, J_d = 4.5, J_q = 6.8), 4.22 (dd, 1, *J* =6.6, 8.6), 4.00 (*dd*, 1, *J* = 8.8), 2.50 (*dd*, 1, *J* = 6.6, 8.8), 1.10 (*d*, 3, *J* = 6.6), 0.43 (*s*, 3), 0.35 (*s*, 3). ^{13}C NMR δ 135.16, 131.32, 129.42, 107.51, 88.73, 84.32, 71.12, 34.87, 16.85, 0.44, -1.60.

trans–**7**: mp 73-75°C. ^{1}H NMR δ 7.49 (*m*, 2), 7.21 (*m*, 3), 5.06 (*s*, 1), 4.42 (*dd*, 1, *J* = 10.0, 8.1), 4.37 (*dd*, 1, *J* = 11.4, 8.1), 3.89 (*dd*, 1, *J* = 7.0, 10.7), 3.77 (*dd*, 1, *J* = 7.0, 10.7), 2.30 (*dd*, 1, *J* = 10.0, 11.3), 1.38 (*s*, 3), 0.75 (*t*, 3, *J* = 7.1, CH_3), 0.36 (*s*, 3), 0.31 (*s*, 3). ^{13}C NMR δ 170.59, 143.91, 128.26, 127.21, 126.00, 95.58, 91.65, 85.53, 73.81, 62.13, 37.57, 23.55, 13.79, 0.11, -2.63.

cis-**8**: $[\alpha]_D^{33}$ +27.8 (*c* 1.046, $CHCl_3$). ^1H NMR δ 7.25 (*m*, 5), 4.77 (*d*, 1, *J* = 3.5), 4.47 (*dd*, 1, *J* = 10.1, 8.0), 4.42 (*dd*, 1, *J* = 11.0, 8.0), 4.25 (*q*, 2, *J* = 7.1), 3.89 (*dt*, 1, *J* = 3.4, 6.6), 2.73 (*t*, 2, *J* = 7.7), 2.42 (*dd*, 1, *J* = 11.0, 10.1), 1.97 (*m*, 2), 1.30 (*t*, 3, *J* = 7.1), 0.38 (*s*, 3), 0.32 (*s*, 3). ^{13}C NMR δ 170.7, 141.9, 128.9, 126.4, 95.98, 86.23, 78.19, 74.62, 62.80, 35.92, 32.43, 28.61, 14.54, 0.25, -2.62.

trans-**8**: $[\alpha]_D^{33}$ -25.6 (*c* 1.027, $CHCl_3$). ^1H NMR δ 7.25 (*m*, 5), 4.84 (*d*, 1, *J* = 3.3), 4.39 (*dd*, 1, *J* = 9.5, 8.40), 4.32 (*dd*, 1, *J* = 9.6, 8.4), 4.28 (*q*, 2, *J* = 7.1), 4.07 (*ddd*, 1, *J* = 8.8, 5.4, 3.3), 2.82 (*ddd*, 1, *J* = 14.0, 9.5, 6.2), 2.74 (*ddd*, 1, *J* = 14.0, 8.9, 7.0), 2.43 (*t*, 1, *J* = 9.5), 2.10 (*m*, 1), 1.88 (*m*, 1), 1.32 (*t*, 3, *J* = 7.1), 0.35 (*s*, 3), 0.32 (*s*, 3). ^{13}C NMR δ 170.8, 141.7, 129.0, 128.9, 126.4, 93.87, 90.21, 85.90, 73.12, 62.90, 36.94, 33.63, 32.13, 14.53, 0.50, -1.96.

cis-**9**: $[\alpha]_D^{35}$ +28.0 (*c* 1.895, $CHCl_3$). ^1H NMR δ 7.98 (*d*, 2), 7.63 (*dd*, 1), 7.50 (*dd*, 2), 7.22-7.05 (*m*, 5), 5.01 (*d*, 1, *J* = 3.3), 4.34 (*dd*, 1, *J* = 8.1, 11.3), 4.28 (*dd*, 1, *J* = 8.1, 10.6), 3.40 (*dt*, 1, *J* = 3.5, 6.8), 2.62 (*dd*, 2, *J* = 6.6, 9.1), 2.52 (*dd*, 1, *J* = 10.6, 11.3), 1.89 (*m*, 2), 0.46 (*s*, 3), 0.35 (*s*, 3). ^{13}C NMR δ 141.1, 134.8, 134.7, 130.8, 129.0, 128.5, 128.3, 126.1, 109.4, 83.06, 78.22, 74.61, 33.85, 31.72, 27.96, -0.30, -2.87.

trans-**9**: $[\alpha]_D^{35}$ -5.5 (*c* 1.400, $CHCl_3$). ^1H NMR δ 8.02 (*d*, 2), 7.61 (*dd*, 1), 7.53 (*dd*, 2), 7.28-7.05 (*m*, 5), 5.07 (*d*, 1, *J* = 4.0), 4.21 (*dd*, 1, *J* = 7.2, 8.4), 4.12-3.98 (*m*, 3), 2.71-2.48 (*m*, 3), 1.70 (*m*, 2), 0.45 (*s*, 3), 0.33 (*s*, 3). ^{13}C NMR δ 140.9, 134.8, 134.7, 130.9, 129.1, 128.5, 128.4, 126.1, 107.3, 87.15, 86.46, 71.18, 34.54, 32.37, 31.38, -0.05, -2.05.

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10. Under the same conditions, aldehydes bearing a acetoxy-, benzoyloxy-, chloroacetoxy-, trichloroacetoxy, or a trifluoroacetoxy group on the α-carbon did not give ring closure, while α-mesyloxyaldehydes gave similar results to α-tosyloxyaldehydes in both yields and diastereoisomeric ratios of the products.
11. This value was calculated following: Bertz, S. H.; Sommer, T. J. *Applications of Graph Theory to Synthesis Planning: Complexity, Reflexivity, and Vulnerability.* In Organic Synthesis: Theory and Applications; Hudlicky, T. Ed.; JAI Press Inc.: Greenwich, CT, **1993**, Vol. 2, p. 67-92.
12. Proton and ^{13}C NMR were recorded at 300 and 75.4 MHz respectively, in $CDCl_3$ solvent. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and coupling constants are expressed in hertz