Diastereoselective transannular [2+2] photocycloaddition of ascorbic acid derivatives

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Dedicated with best wishes to Professor Steven V. Ley on the occasion of his 60th birthday.

Abstract— Ring-closure metathesis of bis-*O,O*-alkenyl ascorbic acid derivatives affords cyclic ethers in good yields which can be further converted by irradiation at 254 nm into new polyoxacyclic structures according to a diastereoselective transannular [2+2] photocycloaddition.

Among all photochemical processes, [2+2] cycloadditions between enones and alkenes are probably the most applied in total synthesis.¹ In particular, intramolecular reactions of substrates bearing both the chromophore and the alkenyl moiety have been widely investigated. By this way, an atom economy is guaranteed and more importantly, high regio- and/or diastereoselectivity can be generally achieved.² Moreover, in order to control the absolute configuration on the cyclobutane ring, diastereoselective³ and also enantioselective⁴ reactions have been recently reported. In connection with our interest in asymmetric photochemical reactions,^{3, 5} we have now considered [2+2] cycloadditions of ascorbic acid derivatives. There are some precedents in the literature concerning photocycloadditions of fonctionalized furanones⁶⁻⁷. For example, Kemmler and Bach showed recently that alkenyl tetronates delivered cycloadducts in good yields but also with impressive diastereoselectivities.⁸ To date, L-ascorbic acid has not been considered as a chiral scaffold for stereoselective [2+2] cycloadditions. Only Paterno-Büchi and photoreduction have been scarcely described by Kulkarni *et al.*⁹ In this study, we focused particularly on transannular cycloadditions of ascorbic acid derivatives, which could lead to polycyclic structures in one single step with high diastereocontrol (Scheme 1). Furthermore, these chiral cyclobutanes could be converted as potential strained ligands or catalysts for various asymmetric reactions like already mentioned in the literature for related structures.¹⁰ To our knowledge, transannular cycloadditions have been essentially studied in Diels-Alder reactions¹¹ and far less for cyclobutane formation.¹² While metathesis ring closure has totally revolutionized the strategy to prepare cycloalkenes,¹³⁻¹⁴ access to suitable substrates for transannular cycloadditions is nowadays easier. For example, Shair *et al.* applied the sequence metathesis / transannular Diels Alder reaction in a straightforward and elegant synthesis of longithorone A.¹⁵

Scheme 1

Depending on the nature of the linkers X and Y, the synthesis of the required substrates was achieved with moderate yields by bis-alkylation,¹⁶ bis-acylation with 3-butenic acid¹⁷ or regioselective monoalkylation / esterification of 5,6-alkylidene ascorbic acids **1a** and **1b** (Scheme 2 – Table 1).

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Scheme 2

Table 1. Alkylation/esterification of ascorbic acid derivatives **1**.

Substrate	X	n	Y	Product	Yield (%)
1a	CH ₂	0	CH ₂	2a	13
1a	CH ₂	1	CH ₂	2b	43
1b	CH ₂	1	CH ₂	2c	19
1a	CO	1	CO	3	42
1a	CH ₂	1	CO	4	42

Compounds **2a-c** were respectively converted into cyclic bisethers **7a-c** in the presence of catalytic amounts of Grubbs' type I catalyst **6a**. (Scheme 3 - Table 2).

Scheme 3

Table 2. RCM of ethers **2a-c** and esters **3-4**.

Substrate	X, Y	n	Product	Yield (%)
2a	CH ₂ /CH ₂	0	(Z)- 7a	50 ^a
2b	CH ₂ /CH ₂	1	(Z)- 7b	66
2c	CH ₂ /CH ₂	1	(Z)- 7c	55
3	CO/CO	1	8	-
4	CH ₂ /CO	1	9	-

^a Reaction performed in the presence of 8.5mol % of **6a**.

The Z-configuration of the new double bond was assigned for steric reasons to all products **7** and was supported by previous results reported in the literature.¹⁸ Under the same metathesis conditions, bisester **3** was totally recovered even after a long time of reaction. This lack of reactivity could be attributed to an unfavourable conformation resulting from electronic repulsions between oxygen atoms of the carboxylic groups or also to an intramolecular complexation of the carbene with the carboxylic group and formation of non productive species.^{13,19} The use of Grubbs second generation catalyst did not improve the reactivity.

The transannular cycloaddition of metathesis products was next investigated (Scheme 4 – Table 3). By using the conditions already advocated by Bach,⁸ the irradiation was performed at 254 nm and at 5°C, in dichloromethane or in acetonitrile and at low concentration (10⁻² M) to avoid oligomerization. The reaction was followed by TLC under total disappearance of the starting material. As in numerous intramolecular [2+2] photocycloadditions, the efficiency of the reaction was mainly due to the length of the unsaturated side chain.

Scheme 4

While no cycloaddition occurred with **7a** which can be explained by the highly unfavourable formation of a tricyclo[2.2.0]octane, irradiation of **7b** afforded in a very high yield only two diastereoisomers identified as the straight adducts **10b** and **11b**.²⁰ They were easily separated by flash-chromatography and a careful NMR study (including nOe) allowed the attribution of the relative and therefore absolute configuration for each compound. The change of the acetonide by a larger group like a cyclohexylidene seems to have a little incidence on the diastereoselectivity as noticed with **10c** and **11c**. By analogy, unprotected compound **7d** conveniently prepared by hydrolysis of **7b**, delivered two tetracyclic diols in quantitative yield which were directly converted into **10b** and **11b**. Interestingly, it appears that the sense of the induction can be simply inverted by protecting or not the lateral 1,2-diol subunit.

Table 3. Photocycloaddition of compounds **7a-d**.

Substrate	R', R'	n	Products 10 / 11 (ratio)	Overall Yield (%)
7a	isopropylidene	0	-	0
7b	isopropylidene	1	10b/11b (47/53)	98
7c	cyclohexylidene	1	10c/11c (59/41)	80
7d^a	H, H	1	10d/11d (32/68) ^b	99

^a Prepared by careful hydrolysis of **7b**.

^b Ratio determined after derivatisation into **10b/11b**.

In order to enhance the diastereoselectivities and to determine the role of the lateral subunit, the reaction was also performed starting from D-(-)-isoascorbic acid derivative **2b'**, an epimer of the parent compound **2a**. Ring-closing metathesis occurred with a similar efficiency and irradiation delivered the polycyclic structures **10b'/11b'** in good yield and exactly the same level of induction (57/43) (Scheme 5). Therefore, it appears that the selectivity of the photocycloaddition is essentially controlled by the stereogenic center C4 contiguous to the C=C bond of the butenolide framework.

Scheme 5

In conclusion, starting from readily available substrates prepared from L-ascorbic acid, we have developed a short access to chiral polyoxacyclic compounds by a two step procedure including a RCM followed by a stereoselective transannular [2+2] photocycloadditions. Compounds **10** and **11** appear as potential candidates for application in enantioselective reactions. Work is now underway to generalize the reaction to parent substrates and to test the products as chiral ligands for enantioselective reactions.

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- 21 The spectroscopic data (¹H, ¹³C-NMR, HRMS) for all compounds are compatible with the proposed structures.

O-Alkylation of ascorbic acid acetonide **1a:** In a two necked flask, K₂CO₃ (62.5 mmol) was added to a solution of **1a** (25 mmol) already dissolved in 2-butanone (50ml). The resulting suspension was heated to 80°C for 15 mn. Unsaturated bromide (57 mmol) and a catalytic amount of nBu₄NI (5mmol) were next added and the mixture was heated under reflux for 12h. After filtration and concentration under vacuum, the solution was washed with brine (15ml) and extracted with ether (2x 30ml). The organic layers were dried over MgSO₄. After filtration and concentration, the product **2** was purified by flash-chromatography over silica. Eluent (AcOEt/PE : 18/82). Compound **2a** : 0.151g. Yield = 12%. R_f = 0.63 (AcOEt/hexanes : 30/70). ¹H-NMR (300 MHz, CDCl₃): δ = 1.32 (s, 3H), 1.38 (s, 3H), 4.00-4.18 (m, 2H), 4.28 (dt, 1H, *J* = 6.7 and 3.8 Hz), 4.54 (d, 1H, *J* = 3.8 Hz), 4.53-4.69 (m, 2H), 4.88 (d, *J* = 6.4Hz, 2H), 5.20-5.45 (m, 4H), 5.82-6.07 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ = 25.5, 25.8, 65.5, 71.3, 71.5, 74.3, 74.9, 110.5, 117.5, 117.9, 121.9, 133.5, 134.5, 156.0, 169.3. Compound **2b** : ¹H-NMR (300MHz, CDCl₃): δ = 1.28 (s, 3H), 1.33 (s, 3H), 2.39 (dt, 4H, *J* = 6.9 Hz), 3.96 (dd, 1H, *J* = 8.5 and 6.4 Hz), 4.04-4.14 (m, 2H), 4.16-4.25 (m, 2H), 4.37-4.46 (m, 3H), 5.00-5.17 (m, 4H), 5.66-5.92 (m, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ = 25.8, 26.2, 34.0, 34.3, 65.5, 71.3, 71.5, 74.3, 74.9, 110.5, 117.5, 117.9, 121.9, 133.5, 134.5, 156.0, 169.3. [α]_D²⁰ = +33 (1.0, CH₂Cl₂).

Ring-closing metathesis: Typical procedure: In a two-necked flask equipped with a cooler, a solution of substrate **2** (1 mmol) in CH₂Cl₂ (100ml) was bubbled with an argon stream for 10 min. Grubbs' catalyst **6a** (2.5% mol) was added at once and the resulting purple solution was heated to 50°C for 2h. After 4h and TLC control, a second addition of catalyst (2.5%) was achieved. After complete disappearance of the starting material, the solvent was removed by concentration and the product purified by flash-chromatography. Prepared from **2a** (160 mg, 0.54 mmol) in the presence of Grubbs catalyst **6a** (38 mg, 8.5 mol%). Yield : 66 %. R_f = 0.16 (30% AcOEt). F = 90-92 °C. **7a** (72 mg). ¹H-NMR (300 MHz, CDCl₃): δ = 1.33 (s, 3H), 1.37 (s, 3H), 3.98-4.28 (m, 3H), 4.57-4.77 (m, 3H), 4.92-4.98 (dd, 1H, *J* = 6.4 Hz), 5.12-5.18 (d, 1H, *J* = 5.1Hz), 6.17 (m, 2H, CH=CH₂). ¹³C-NMR (75 MHz, CDCl₃): δ = 25.7, 26.1, 65.9, 65.4, 74.3, 74.6, 74.8, 110.6, 121.7, 122.2, 136.9, 161.0, 169.2. HRMS : Calcd pour C₁₃H₁₆O₇+1 = 269.1025. Found = 269.1025. Prepared from **2b** (1.250 g, 3.8 mmol) in the presence of Grubbs catalyst **6a** (180 mg, 6 mol%). Yield : 66 %. R_f = 0.30 (AcOEt: PE: 20/80). **7b** (750 mg). ¹H-NMR (300 MHz, CDCl₃): δ = 1.38 (s, 3H), 1.42 (s, 3H), 2.39-2.70 (m, 4H), 4.02-4.25 (m, 3H), 4.27-4.35 (m, 2H), 4.52 (d, 1H, *J* = 3.2 Hz), 4.56-4.79 (m, 2H), 5.65-5.76 (m, 2H, CH=CH). ¹³C-NMR (75 MHz, CDCl₃): δ = 25.9, 26.3, 26.8, 28.5, 65.6, 69.2, 71.7, 74.3, 75.0, 110.6, 121.1, 157.7, 128.1, 130.7, 169.5. HRMS calcd for C₁₅H₂₀O₇ = 296.1260. Found = 296.1262. [α]_D²⁰ = +40 (1.0, CH₂Cl₂).

Transannular cycloaddition: Typical procedure: Substrate **7b** (0.310g) was dissolved in acetonitrile (105 ml) and pored into quartz irradiation tubes fitted with a septum. After deoxygenated with a stream of dry nitrogen, the solution was irradiated at 254 nm at 10°C until complete conversion (typically 6h). After concentration, the two diastereoisomers were separated by flash-chromatography (eluent AcOEt/PE 40/60). Compounds **10b** and **11b** isolated from the irradiation of **7b** (250 mg) after concentration and flash-chromatography on silica (eluent : AcOEt/PE : 40/60). **10b** 111 mg (R_f = 0.37 - Eluent : AcOEt/PE : 40/60). ¹H-NMR (300MHz, CDCl₃): δ = 1.42 (s, 3H), 1.45 (s, 3H), 1.94-2.18 (m, 4H), 3.11 (dt, 1H, *J* = 8.0 Hz and 4.9 Hz), 3.33 (dt, 1H, *J* = 9.5Hz and 4.9 Hz), 3.95 (t, 1H, *J* = 7.5 Hz), 4.02-4.18 (m, 3H), 4.27-4.36 (m, 3H), 4.49 (d, 1H, *J* = 3.7Hz). ¹³C-NMR (75 MHz, CDCl₃): δ = 26.3, 26.4, 26.3, 26.4, 37.5, 40.2, 65.9, 71.2, 74.6, 75.0, 81.5, 83.2, 84.2, 110.8, 175.8 (C=O). HRMS : calcd for C₁₅H₂₀O₆+1 = 297.1338. Found = 297.1337. m.p. = 152°C. [α]_D²⁰ = +54.9 (0.5, CH₂Cl₂). **11b** 123 mg (R_f = 0.14 - Eluent : AcOEt/PE : 40/60) ¹H-NMR (300MHz, CDCl₃): δ = 1.30 (s, 3H), 1.36 (s, 3H), 1.95-2.05 (m, 4H), 2.80-92 (m, 1H), 2.99-3.07 (dt, 1H, *J* = 8.0 Hz and 6.9 Hz), 3.8-9 (m, 1H), 4.02-11 (m, 3H), 4.12-28 (m, 3H), 4.32-37 (m, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ = 26.4, 26.7 (p); 26.4, 26.7 (s); 41.3, 42.6 (s); 66.0 (s); 72.8, 74.4 (s); 74.2, 82.4 (t); 81.2, 82.4 (t); 111.1 (q); 176.1 (C=O). HRMS : calcd for C₁₅H₂₀O₆+1 = 297.1338. Found = 297.1335. F = 132°C. [α]_D²⁰ = +48.7 (0.5, CH₂Cl₂).