Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 733–736
Tetrahedron Letters

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

Sébastien Redon and Olivier Piva*

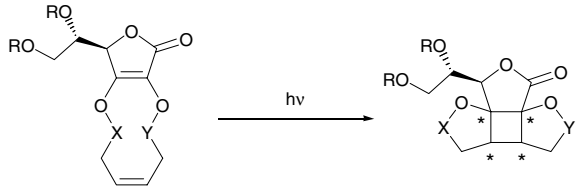
Université LYON I—UMR CNRS 5181, Laboratoire de Chimie Organique, Photochimie et Synthèse, Bat. Raulin/4–43, Bd du 11 novembre 1918, 69622 Villeurbanne cedex, France

Received 14 September 2005; revised 16 November 2005; accepted 21 November 2005
Available online 7 December 2005

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

Abstract—Ring-closing 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, diastereoselective[3] and also enantioselective[4] 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 functionalized furanones.[6,7] 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 and co-workers.[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



Scheme 1.

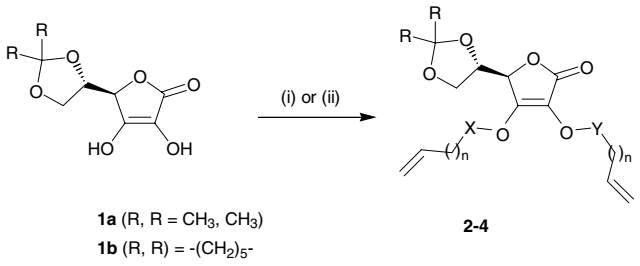
catalysts for various asymmetric reactions as already mentioned in the literature for related structures.[10] To our knowledge, transannular cycloadditions have been essentially studied in Diels–Alder reactions[11] and far less for cyclobutane formation.[12] While ring closing metathesis has totally revolutionized the strategy to prepare cycloalkenes,[13,14] access to suitable substrates for transannular cycloadditions is nowadays easier. For example, Shair and co-workers applied the sequence metathesis/transannular Diels–Alder reaction in a straightforward and elegant synthesis of longithorone A.[15]

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-butenoic acid[17] or regioselective monoalkylation/esterification of 5,6-alkylidene ascorbic acids **1a** and **1b** (Scheme 2, Table 1).

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).

* Corresponding author. Tel./fax: +33 (0)472 448 136; e-mail: piva@univ-lyon1.fr

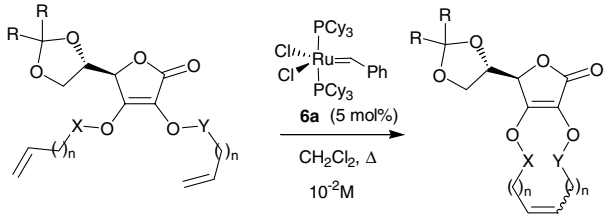
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.102



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



Scheme 3.

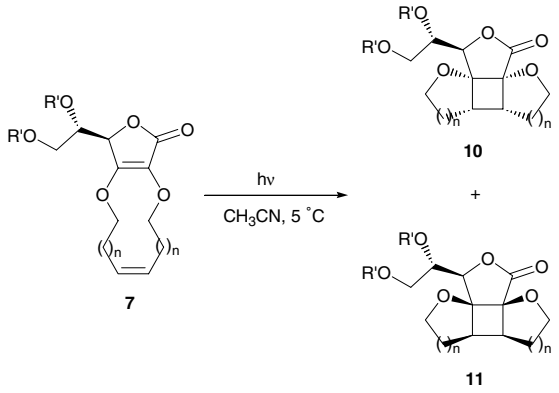
Table 2. RCM of ethers **2a–c** and esters **3–4**

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 8.5 mol % 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 unfavorable 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 nonproductive 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 Kemmler and Bach,[8] the irradiation was performed at 254 nm at 5 °C, in dichloromethane or in acetonitrile and at low



Scheme 4.

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

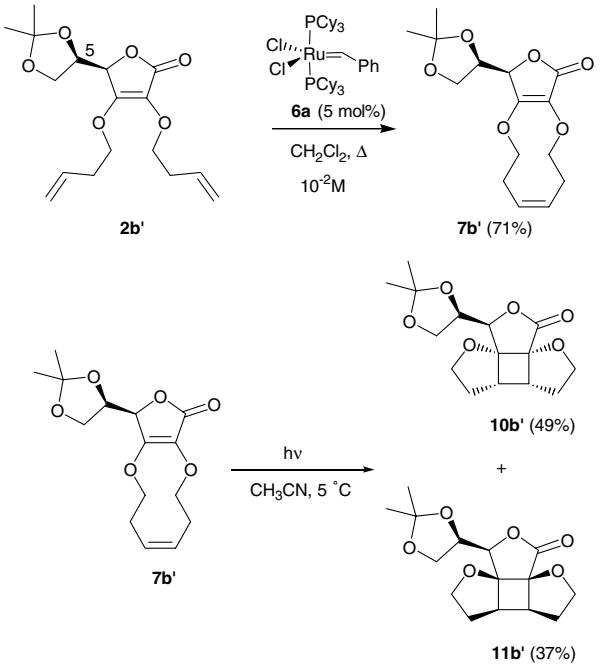
Substrate	*R*′, *R*′	*n*	Products **10/11** (ratio)	Overall yield (%)
7a	Isopropylidene	0	—	0
7b	Isopropylidene	1	**10b/11b** (47/53)	98
7c	Cyclohexylidene	1	**10c/11c** (59/41)	80
7d[a]	H, H	1	**10d/11d** (32/68)[b]	99

[a] Prepared by careful hydrolysis of **7b**.
[b] Ratio determined after derivatization into **10b/11b**.

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.

While no cycloaddition occurred with **7a**, which can be explained by the highly unfavorable 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 inversed by protecting or not the lateral 1,2-diol subunit.

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



Scheme 5.

controlled by the stereogenic center C4 contiguous to the C=C bond of the butenolide framework.

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.[21] 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.

References and notes

1. (a) Fleming, S. A.; Bradford, C. L.; Gao, J. J. In *Molecular and Supramolecular Photochemistry: Organic Photo-chemistry*; Ramamurthy, V., Schanze, V., Eds.; Dekker: New York, 1997; Vol. 1, pp 187–243; (b) Pete, J. P. *Adv. Photochem.* **1996**, *21*, 135–216; (c) Bach, T. *Synthesis* **1998**, 683–703; (d) Margaretha, P. In *Synthetic Organic Photochemistry*; Griesbeck, A. G., Mattay, J., Eds.; Dekker: New York, 2004; Vol. 12, pp 211–237.
2. (a) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297–588; (b) Grosch, B.; Bach, T. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 61.
3. Faure, S.; Piva-Le Blanc, S.; Bertrand, C.; Pete, J. P.; Faure, R.; Piva, O. *J. Org. Chem.* **2002**, *67*, 1061–1070.
4. (a) Chen, C.; Chang, V.; Cai, X.; Duesler, E.; Mariano, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 6433–6434; (b) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982–7990; (c) Griesbeck, A. G.; Meierhenrich, U. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3147–3154.
5. Bargiggia, F.; Dos Santos, S.; Piva, O. *Synthesis* **2002**, 427–437.
6. For intermolecular photocycloadditions of furanones: (a) Takamatsu, K.; Ryang, H.-S.; Sakurai, H. *J. Org. Chem.* **1976**, *41*, 541–543; (b) Witiak, D. T.; Newman, H. A. I.; Poochikian, G. K.; Fogt, S. W.; Baldwin, J. R.; Sober, C. L.; Feller, D. R. *J. Med. Chem.* **1978**, *21*, 833–837; (c) Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1985**, *50*, 4707–4711.
7. For intramolecular [2+2]: (a) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1994**, *50*, 12829–12842; (b) Bach, T.; Kemmler, M.; Herdtweck, E. *J. Org. Chem.* **2003**, *68*, 1994–1997, and references cited therein.
8. (a) Kemmler, M.; Bach, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4824–4826; (b) Kemmler, M.; Herdtweck, E.; Bach, T. *Eur. J. Org.* **2004**, 4582–4595.
9. (a) Thopate, S. R.; Kulkarni, M. G.; Puranik, V. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1110–1112; (b) Kulkarni, M. G.; Kate, S. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4242–4244.
10. For the synthesis and applications of cyclobutane derivatives in asymmetric reactions, see: (a) Massonneau, V.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **1976**, *27*, 5497–5498; (b) Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* **1989**, 542–547; (c) Dulcère, J.-P.; Crandall, J.; Faure, R.; Santelli, M.; Agati, V.; Mihoubi, M. N. *J. Org. Chem.* **1993**, *58*, 5702–5708; (d) Morimoto, T.; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 75–78; (e) Haag, D.; Scharf, H.-D. *J. Org. Chem.* **1996**, *61*, 6127–6135; (f) Hayashi, M.; Hashimoto, Y.; Takezaki, H.; Watanabe, Y.; Saigo, K. *Tetrahedron: Asymmetry* **1998**, *9*, 1863–1866.
11. (a) Bilodeau, F.; Dube, L.; Deslongchamps, P. *Tetrahedron* **2003**, *59*, 2781–2791; (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531–13540; (c) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269–5272; (d) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502–7512.
12. (a) Nishimura, J.; Takeuchi, M.; Takahashi, H.; Sato, M. *Tetrahedron Lett.* **1990**, *31*, 2911–2914; (b) White, D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673–9674; (c) Wollenweber, M.; Hunkler, D.; Keller, M.; Knothe, L.; Prinzbach, H. *Bull. Soc. Chim. Fr.* **1993**, *130*, 32–57.
13. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (c) Aitken, S. G.; Abell, A. D. *Aust. J. Chem.* **2005**, *58*, 3–13.
14. Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23.
15. Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.
16. Kulkarni, M. G.; Thopate, S. R. *Tetrahedron* **1996**, *52*, 1293–1302.
17. Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–523.
18. Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
19. Cossy, J.; Bauer, V.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187–4188.
20. (a) Pete, J. P. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, 2004, Chapter 71; (b) Schuster, D. I. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 72.
21. The spectroscopic data (^{1}H, ^{13}C NMR, HRMS) for all compounds are compatible with the proposed structures. *O-Alkylation of ascorbic acid acetonide* **1a**: In a two-necked flask, K_2CO_3 (62.5 mmol) was added to a solution

of **1a** (25 mmol) already dissolved in 2-butanone (50 mL). The resulting suspension was heated to 80 °C for 15 min. Unsaturated bromide (57 mmol) and a catalytic amount of n-Bu_4NI (5 mmol) were next added and the mixture was heated under reflux for 12 h. After filtration and concentration under vacuum, the solution was washed with brine (15 mL) and extracted with ether (2×30 mL). The organic layers were dried over $MgSO_4$. After filtration and concentration, the product **2** was purified by flash-chromatography over silica. Eluent (AcOEt/PE: 18/82). Compound **2a**: 0.151 g. Yield = 12%. $R_f = 0.63$ (AcOEt/hexanes: 30/70). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (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, $J = 6.4$ Hz, 2H), 5.20–5.45 (m, 4H), 5.82–6.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.5$, 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 (300 MHz, $CDCl_3$): $\delta = 1.28$ (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). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.8$, 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. $[\alpha]_D^{20}$ +33 (1.0, CH_2Cl_2).

Ring-closing metathesis: Typical procedure: In a two-necked flask equipped with a cooler, a solution of substrate **2** (1 mmol) in CH_2Cl_2 (100 mL) 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 2 h. After 4 h 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 I **6a** (38 mg, 8.5 mol %). Yield: 66%. $R_f = 0.16$ (30% AcOEt). $F = 90$–92 °C. Compound **7a** (72 mg). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (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, $J = 5.1$ Hz), 6.17 (m, 2H, CH=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.7$, 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 $C_{13}H_{16}O_7+1 = 269.1025$. Found = 269.1025. Prepared from **2b** (1.250 g, 3.8 mmol) in the presence of Grubbs catalyst I **6a** (180 mg, 6 mol %). Yield: 66%. $R_f = 0.30$ (AcOEt/PE: 20/80). Compound **7b** (750 mg). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (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). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.9$, 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 $C_{15}H_{20}O_7 = 296.1260$. Found = 269.1262. $[\alpha]_D^{20}$ +40 (1.0, CH_2Cl_2).

Transannular cycloaddition: Typical procedure: Substrate **7b** (0.310 g) was dissolved in acetonitrile (105 mL) and poured 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 6 h). 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). Compound **10b** 111 mg ($R_f = 0.37$—eluent: AcOEt/PE: 40/60). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 3H), 1.45 (s, 3H), 1.94–2.18 (m, 4H), 3.11 (dt, 1H, $J = 8.0$ and 4.9 Hz), 3.33 (dt, 1H, $J = 9.5$ 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, $J = 3.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.3$, 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 $C_{15}H_{20}O_6+1 = 297.1338$. Found = 297.1337. Mp = 152 °C. $[\alpha]_D^{20}$ +54.9 (0.5, CH_2Cl_2). Compound **11b** 123 mg ($R_f = 0.14$—eluent: AcOEt/PE: 40/60). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ (s, 3H), 1.36 (s, 3H), 1.95–2.05 (m, 4H), 2.80–92 (m, 1H), 2.99–3.07 (dt, 1H, $J = 8.0$ and 6.9 Hz), 3.8–9 (m, 1H), 4.02–11 (m, 3H), 4.12–28 (m, 3H), 4.32–37 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 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 $C_{15}H_{20}O_6+1 = 297.1338$. Found = 297.1335. $F = 132$ °C. $[\alpha]_D^{20}$ +48.7 (0.5, CH_2Cl_2).