JOC Article

Stereocontrolled Photocyclization of 1,2-Diketones: Application of a 1,3-Acetyl Group Transfer Methodology to Carbohydrates

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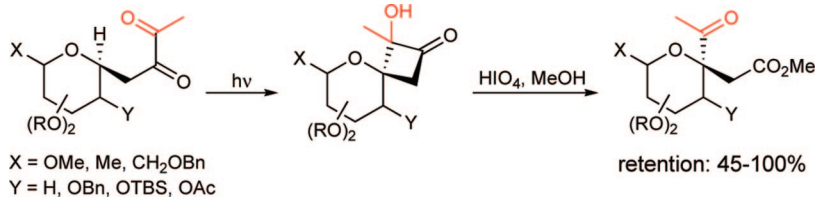

Photolysis of 1-glycosyl-2,3-butanodione derivatives using visible light is a mild and selective procedure for the synthesis of chiral 1-hydroxy-1-methyl-5-oxaspiro[3.5]nonan-2-one carbohydrate derivatives. The results strongly suggest that stereocontrol of the cyclization is dependent on conformational and stereoelectronic factors. Further oxidative opening of the 1-hydroxy-1-methyl-2-cyclobutanone moiety affords new *C*-ketoside derivatives either in *C*- and *O*-glycoside series. This tandem two-step process could be considered to be a stereocontrolled 1,3-transference of an acetyl group, and it can be applied either to pyranose and furanose models.

Introduction

The development of efficient methods to generate regio- and stereocontrolled C−C bonds under mild conditions, especially when constructing quaternary stereocenters, is highly important in synthetic organic chemistry.[1] Norrish-Yang photocyclization has been used to accomplish this task, aliphatic and aromatic ketones and α-keto esters being the most widely used reactants.[2]

On the other hand, although the Norrish-Yang photocyclization of 1,2-diketones to generate 2-hydroxy-cyclobutanones has been well studied since the early 60s,[3] only a few reports on the use of this methodology appears in the literature[3a,4] and, as far as we know, only one case involved a chiral substrate.[5] Diastereoselective C−C bond formation, absence of competitive cleavage reactions[6] or additional reagents, high yields, and possible use of sunlight are the most attractive features of this methodology for the synthetic chemist and render exploring its scope and limitations highly interesting.

Herein, we expand a previous report[7] on the highly efficient use of a Norrish-Yang photocyclization to obtain new spirocyclic monosaccharide-derivatives of types **III** and **IV** via a hydrogen atom transfer (HAT) reaction promoted by a 1,2-diketone **I**, in its excited state, followed by C−C tetrasubstituted bond formation in a diastereoselective manner (Scheme 1). Of special interest is the study of the tendency to inversion at C-5,[8] probably triggered by conformational changes that the 1,4-

(1) For recent reviews on the construction of quaternary carbon stereocenters, see: (a) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (b) García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, B., Eds.; Wiley-VCH: Weinheim, 2005. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (g) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (h) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (i) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (j) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (k) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(2) For reviews on Norrish-Yang, see: (a) Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83. (b) Wagner, P. J.; Park, B. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; p 227. (c) *Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2003; Chapters 52, 55, 57, and 58. (d) Wagner, P. J. In *Synthetic Organic Photochemistry (Molecular and Supramolecular Photochemistry)*; Griesbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2005; Vol. 12, p 11. (e) Wessig, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 523. (f) Wessig, P.; Muehling, O. *Eur. J. Org. Chem.* **2007**, 2219.

(3) (a) Urry, W. H.; Trecker, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 118. (b) Urry, W. H.; Trecker, D. J.; Winey, D. A. *Tetrahedron Lett.* **1962**, *3*, 609. (c) Turro, N. J.; Lee, T.-J. *J. Am. Chem. Soc.* **1969**, *91*, 5651. (d) Urry, W. H.; Duggan, J. C.; Pai, M.-S. H. *J. Am. Chem. Soc.* **1970**, *92*, 5785.

(4) (a) Hamer, N. K. *J. Chem. Soc., Perkin Trans.* **1979**, *1*, 1285. (b) Hamer, N. K. *Tetrahedron Lett.* **1982**, *23*, 473. (c) Hamer, N. K. *J. Chem. Soc., Perkin Trans.* **1983**, 61. (d) Hamer, N. K. *Tetrahedron Lett.* **1986**, *27*, 2167.

(5) Obayashi, M.; Mizuta, E.; Noguchi, S. *Chem. Pharm. Bull.* **1979**, *27*, 1679.

(6) Yang, N. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913.

(7) Herrera, A. J.; Rondón, M.; Suárez, E. *Synlett* **2007**, 1851.

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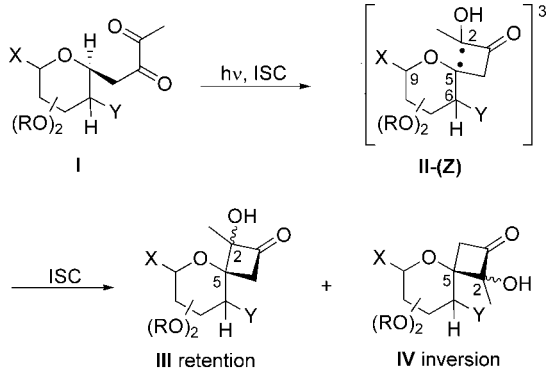
SCHEME 1. Mechanism of Photocyclization[13]



diradical intermediate **II** undergoes in its triplet state, within its lifetime,[9] before the intersystem crossing (ISC) occurs.

In this regard, we probe different substituents and stereochemistries, mainly at positions 5, 6, and 9 of the pyranose core of **II-(Z)**, to explore the role of the stereoelectronic interactions,[9b,10] conformational restrictions,[11] and formation of intramolecular hydrogen bonds[12] in the stereocontrol of this reaction.

It has been reported that 1,2-diketones mainly abstract hydrogen atoms from their triplet state and with a very small rate constant related to alkyl and aryl ketones.[3c] However, in our cases, the reactions were accomplished within relatively short times. A new factor has been introduced in these models. The presence of the geminate endocyclic oxygen may specially activate the hydrogen atom transference. Furthermore, the 1,4-diradical intermediate **II** may be stabilized by a possible conjugative stabilizing interaction of the SOMO-C5 radical with the lone pair at the ring oxygen and the σ^*-LUMO of the C6−O bond (if Y = OR)[10] affecting probably the rate of the HAT step and the lifetime of intermediate **II**. To the best of our knowledge, such studies have not so far been carried out, although this C5-centered radical resembles the in-depth studied anomeric radical[14] where the C5–H bond has been replaced by a C5–alkyl; thus, it will be termed a pseudoanomeric radical. The photochemical generation of a pseudoanomeric radical at C5 of the ribose moiety of a nucleotide, mimicking the 4′-RNA and 4′-DNA radicals, has previously been achieved via a Norrish type I cleavage to study the DNA and RNA damage.[15]

Additionally, we have recently shown that the relatively unstable 2-hydroxy-cyclobutanones can be converted into much more stable methyl-γ-ketoesters fused to the carbohydrate skeleton by treatment with periodic acid in methanol following previously reported procedures (as described in Scheme 4).[3d,4b] The two-step tandem process (photocyclyzation followed by oxidative opening and methyl esterification) can be considered to be a methodology to achieve a rather interesting diastereocontrolled C→C-[1,3]-acetyl shift. This methodology has been shown to tolerate various functional and protecting groups used in carbohydrate chemistry expanding its applications in organic synthesis.

Results and Discussion

With the aim of rationalizing the role of the stereoelectronic and conformational factors in the stereocontrol of this process, we have synthesized a number of pyranose and furanose models carrying a four-carbon 1,2-diketone tether and submitted to various photolysis conditions as shown in Tables 1−2 and Scheme 6.[16]

Preparation of the required 1-glycosyl-2,3-butanodione derivatives was accomplished following three different protocols in which the 1,2-diketone moiety was prepared by oxidation of the corresponding alkyne derivative. The synthesis of compounds **4**, **8**, and **11** are depicted in Scheme 2 as representative examples of each protocol.[17]

The primary bromide of the glucose derivative **1** was substituted by nucleophilic attack of allylmagnesiumchloride in high yield. This alternative methodology was used because a more direct route by nucleophilic substitution either of this bromide, tosylate, or triflate derivatives with 1-propynylmagnesium bromide, ethynylmagnesium chloride, or propargylmagnesium bromide failed in this case. Transformation of the alkene **2** into the alkyne **3** was accomplished by ozonolysis followed by the Corey−Fuchs methodology.[18] Isomerization of the terminal alkyne into the methylalkyne functionality under basic conditions followed by oxidation with the $RuO_2 \cdot H_2O/NaIO_4$ system provided the 1,2-diketone **4** in moderate yields.[19]

A second less efficient alternative procedure to introduce the alkyne functionality modifying the primary (C-6) position of suitably protected pyranose models was employed to obtain **8**. Swern oxidation of the primary alcohol of **5** and subsequent addition of 1-propynylmagnesiumbromide afforded an isomeric mixture of propargyl alcohol **6** in moderate yield. Barton−McCombie radical deoxygenation[20] through the methylxanthate derivative leaded to formation of **7** with 44% of yield, which

(8) For examples of epimerization of anomeric and pseudoanomeric radicals, see: (a) Brunckova, J.; Crich, D.; Yao, Q. *Tetrahedron Lett.* **1994**, *35*, 6619. (b) Yamazaki, N.; Ei-chemberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6626.

(9) For discussions on the lifetime of diradicals in solution, see: (a) Johnston, L. J.; Caiano, J. C. *Chem. Rev* **1989**, *89*, 521. and references cited therein. (b) Cai, X.; Cygon, P.; Goldfuss, B.; Griesbeck, A. G.; Heckroth, H.; Fujitsuka, M.; Majima, T. *Chem.−Eur. J.* **2006**, *12*, 4662.

(10) (a) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H.-G.; Sustman, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (c) Brunckova, J.; Crich, D. *Tetrahedron* **1995**, *51*, 11945. and references cited therein.

(11) (a) Griesbeck, A. G.; Mauder, H.; Stadtmüller, S. *Acc. Chem. Res.* **1994**, *27*, 70. (b) Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885. (c) Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586. and references cited therein. (d) For anomeric effect, see: Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019. and references cited therein. (e) For anomeric effect of proton, see: David, S. *Carbohydr. Res.* **2005**, *340*, 2569.

(12) Walther, K.; Kranz, U.; Henning, H.-G. *J. Prakt. Chem.* **1987**, *329*, 859.

(13) For convenience, the atom-numbering system used throughout this section corresponds to that depicted in structures of Table 1 and the Schemes, although a IUPAC systematic nomenclature has been used in the Supporting Information.

(14) For recent reviews, see: (a) Giese, B.; Zeitz, H.-G. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; p 507. (b) Pearce, A. J.; Mallet, J.-M.; Sinaÿ, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 523.

(15) Strittmatter, H.; Dussy, A.; Schwitter, U.; Giese, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 135.

(16) Three different light sources were used: Sunlight: Direct sunlight: a bright sunny day, on cloudy days the reaction was considerably slower; UV lamp: 450 W ACE-Hanovia medium-pressure mercury lamp in an immersion well with 4.8 mm Pyrex walls; Daylight lamp: Philips lamp (master PL electronic, 23 W/865).

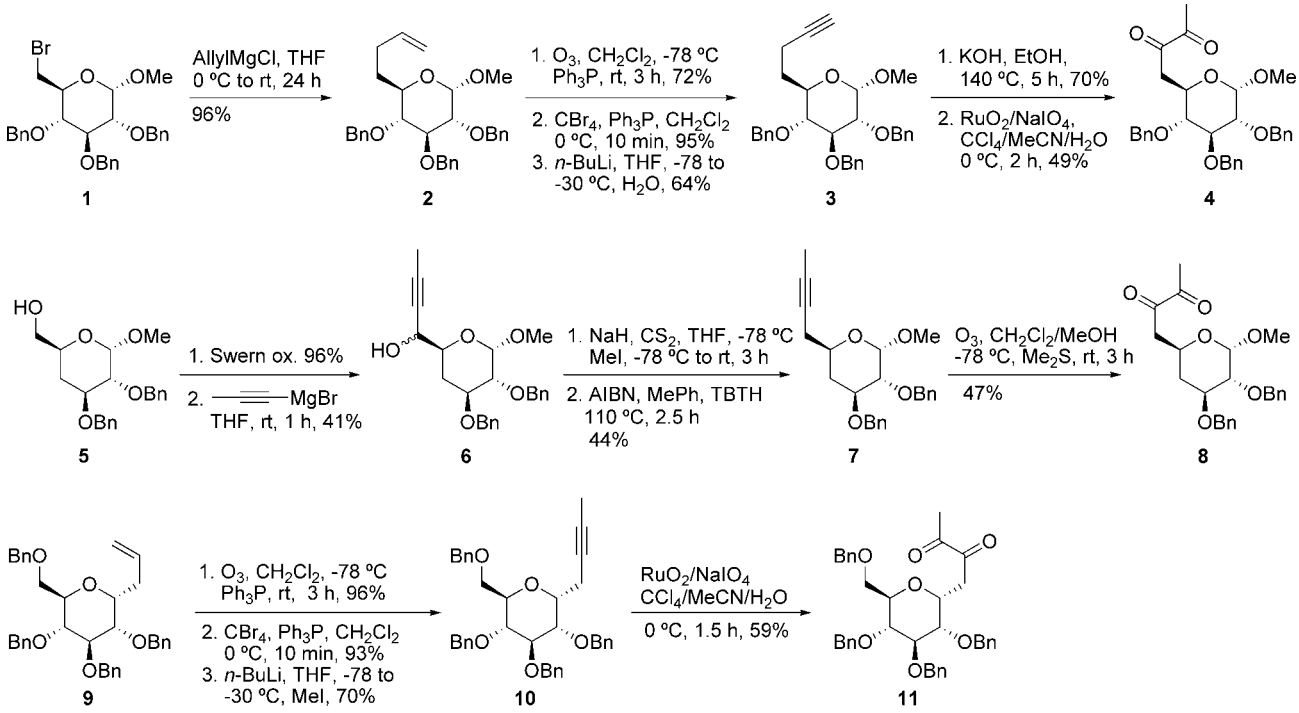
(17) Complete details of the synthesis of all the 1,2-diketone precursors are provided in the Supporting Information.

(18) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

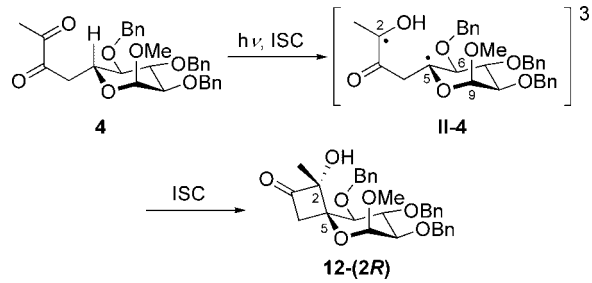
(19) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237.

(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 1574.

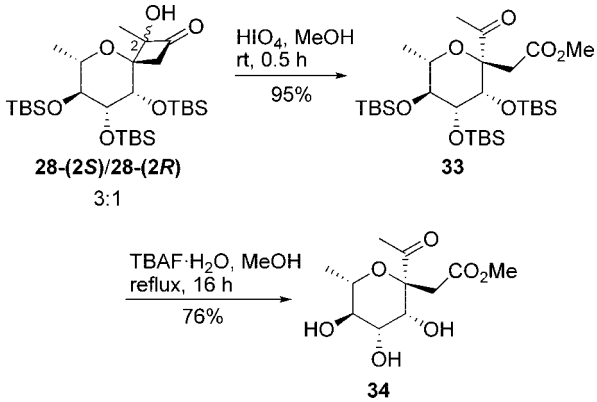
SCHEME 2. Synthesis of 1,2-Diketone Precursors



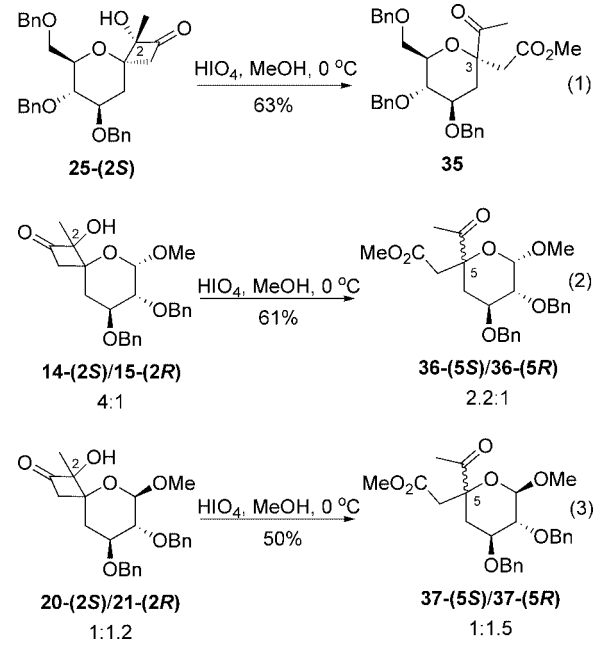
SCHEME 3. Photocyclization of 1,2-Diketone 4



SCHEME 4. Synthesis of *C*-Ketosides



SCHEME 5. Oxidative Opening of 1-Hydroxy-1-methylcyclobutan-2-one Moiety



upon ozonolysis followed by quenching with Me_2S provided the product **8** in moderate yield.[21]

All *C*-glycoside derivatives were efficiently prepared by using a four-step methodology: Lewis acid catalyzed *C*-glycosidation with allyltrimethylsilane[22] followed sequentially by ozonolysis, Corey–Fuchs protocol, and oxidation of the triple bond to obtain the 1,2-diketone moiety as shown for the synthesis of compound **11**.

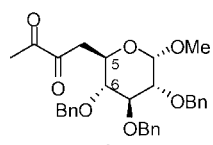
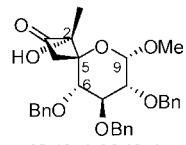
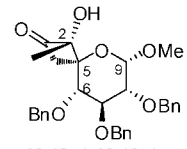
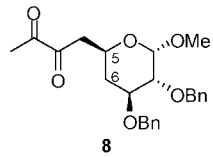
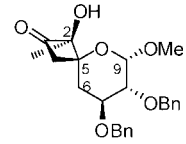
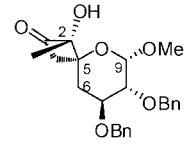
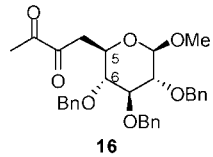
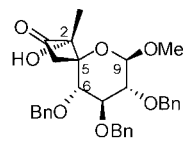
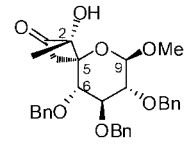
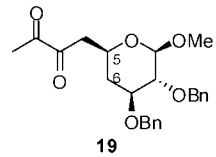
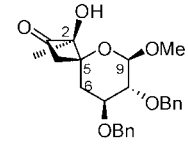
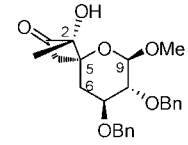
Alternatively, the alkyne moiety was converted into the 1,2-diketone functionality by ozonolysis quenched with Ph_3P for the synthesis of various models.[23] It is important to mention that the yields of formation of the 1,2-diketone moiety, either in pyranose or furanose models, were lower with substrates

(21) Favino, T. F.; Fronza, G.; Fuganti, C.; Fuganti, D.; Graselli, P.; Mele, A. *J. Org. Chem.* **1996**, *61*, 8975.

(22) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, UK, 1995.

(23) The use of Ph_3P instead of Me_2S for this selective oxidation does not have precedents in the literature and resulted in an improved reagent for various models.

TABLE 1. Photocyclization of 1,2-Diketones Derived from *O*-Glycosides via HAT

entry	substrate	light source[a]	solvent	time (h)	retention (A/B)	ratio[b] (A:B:C:D)	inversion (C/D)	yield[c] (%)	retention (%)
	 **4**				 **12-(2*R*)/12-(2*S*)**		 **13-(2*R*)/13-(2*S*)**		
1		SL	neat	21		(1 : 0 : 0 : 0)		42	100
2		SL	$CHCl_3$	2		(1 : 0 : 0 : 0)		quant	100
3		UV	$CHCl_3$	1.5		(1 : 0 : 0 : 0)		quant	100
4		UV	^tBuOH[d]	1.8		(6 : 1 : 1 : 0)		92	87
	 **8**				 **14-(2*R*)/14-(2*S*)**		 **15-(2*R*)/15-(2*S*)**		
5		SL	$CHCl_3$	1.1		(0 : 2.3 : 1 : 0)		61	70
6		UV	$CHCl_3$	0.55		(0 : 2.3 : 1 : 0)		65	70
7		DL	$CHCl_3$	0.55		(0 : 2.3 : 1 : 0)		55	70
8		DL	$CHCl_3$	4		(0 : 3 : 1 : 0)		55	75[e]
	 **16**				 **17-(2*R*)/17-(2*S*)**		 **18-(2*R*)/18-(2*S*)**		
9		UV	$CHCl_3$	0.6		(15 : 6 : 1 : 0)		95	95
10		UV	$CHCl_3$	0.3		(11 : 3 : 1 : 0)		88	93[f]
11		UV	$CHCl_3$	2.0		(1 : 0 : 0 : 0)		80	100[g]
	 **19**				 **20-(2*R*)/20-(2*S*)**		 **21-(2*R*)/21-(2*S*)**		
12		UV	$CHCl_3$	1.1		(0 : 1 : 1.2 : 0)		56	45

[a] SL: sunlight, UV: UV-lamp, DL: daylight-lamp. [b] The ratios and stereochemistries were determined by ^1H NMR of the reaction crudes and NOESY experiments, respectively. For clarity, the underlined major diastereomers are depicted. [c] Yields refer to purified products. [d] *t*-BuOH/$CHCl_3$ (3:1). [e] 0.4 M Naphthalene, 10 mM substrate. [f] 0.5 M Benzophenone, 38 mM substrate. [g] 0.5 M Pyrene, 38 mM substrate.

bearing benzyl groups, being approximately around 50%. In fact, the three above-mentioned procedures to accomplish this alkyne oxidation can be used to oxidize benzyl groups to benzoate groups.[24]

The reaction of photocyclization to obtain the desired spirocompounds were performed by placing the 1,2-diketones in a Pyrex vessel and irradiating with one of the three different light sources[16] emitting in the violet-blue region of the spectrum, employing preferentially deoxygenated solvents. The yields of isolated spirocompounds for this reaction vary between moderate and excellent for all the examples assayed (Tables 1 and 2).

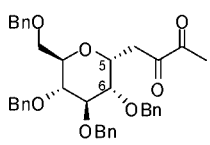
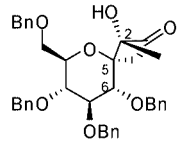
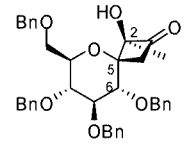
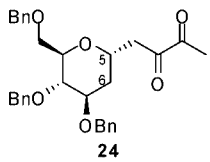
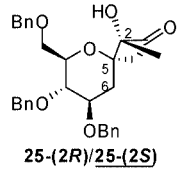
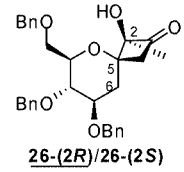
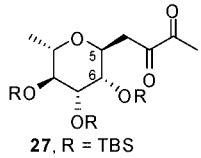
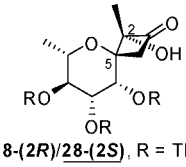
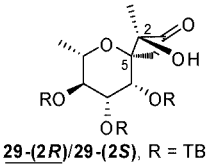
Model **4** was selected due to its conformationally restricted $^4C_1$ pyranose ring.[25] 1,2-Diketone **4** was irradiated with outdoor sunlight in its crystalline form for 20 h until the yellow color faded, affording a mixture of compounds from which the main product **12-(2*R*)** was isolated in moderate yield after silica gel chromatography as a sole stereoisomer (Table 1, entry 1). Side products of photooxidation and intermolecular reactions were formed, probably due to the presence of oxygen, a long reaction time, and restricted mobility of the molecules in the crystalline net. The observed stereocontrol could have been determined by the preorganized media in the crystal;[26] however, a single product **12-(2*R*)** was obtained in quantitative yield upon irradiation with sunlight in solution with $CHCl_3$ or C_6H_6 as solvent (Table 1, entry 2). A slightly shorter time was required upon irradiation with the UV lamp (Table 1, entry 3). The reaction proceeded with total retention at C5. For this model, a C5 radical with very slow isomeric interconversion is formed at the 1,4-diradical intermediate **II-4** stage (Scheme 3). This isomerization is controlled by conformational changes at the

(24) (a) Schuda, P. F.; Cichowicz, M. B. *Tetrahedron Lett.* **1983**, *24*, 3829. (b) Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J.-P. *Synthesis* **1985**, 1123.

(25) The mentioned conformation of substrates was determined by ^1H NMR.

(26) Kaanumalle, L. S.; Natarajan, A.; Ramamurthy, V. In *Synthetic Organic Photochemistry (Molecular and Supramolecular Photochemistry)*; Griesbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2005; Vol. 12, p 553.

TABLE 2. Photocyclization of 1,2-Diketones Derived from*C*-Glycosides via HAT

entry	substrate	light source[a]	solvent	time (h)	retention (A/B)	ratio[b] (A:B:C:D)	inversion (C/D)	yield[c] (%)	retention (%)
	 **11**				 **22-(2*R*)/22-(2*S*)**		 **23-(2*R*)/23-(2*S*)**		
1		UV	$CHCl_3$	1		(1 : 7 : 2 : 2)		90	67
2		SL	neat	2.5		(1 : 6 : 1 : 1.5)		85	74
	 **24**				 **25-(2*R*)/25-(2*S*)**		 **26-(2*R*)/26-(2*S*)**		
3		UV	$CHCl_3$	0.75		(- : 4 : - : -)[d]		64	>77[d]
	 **27**, R = TBS				 **28-(2*R*)/28-(2*S*)**, R = TBS		 **29-(2*R*)/29-(2*S*)**, R = TBS		
4		UV	$CHCl_3$	2.75		(1 : 3 : 0 : 0)		78	100
5		UV	$CHCl_3$	13		(1 : 4 : 0 : 0)		87	100[e]
	30, R = Ac				**31-(2*R*)/31-(2*S*)**, R = Ac		**32-(2*R*)/32-(2*S*)**, R = Ac		
6		UV	$CHCl_3$	0.55		(9 : 3.6 : 1 : 3.8)		88	72

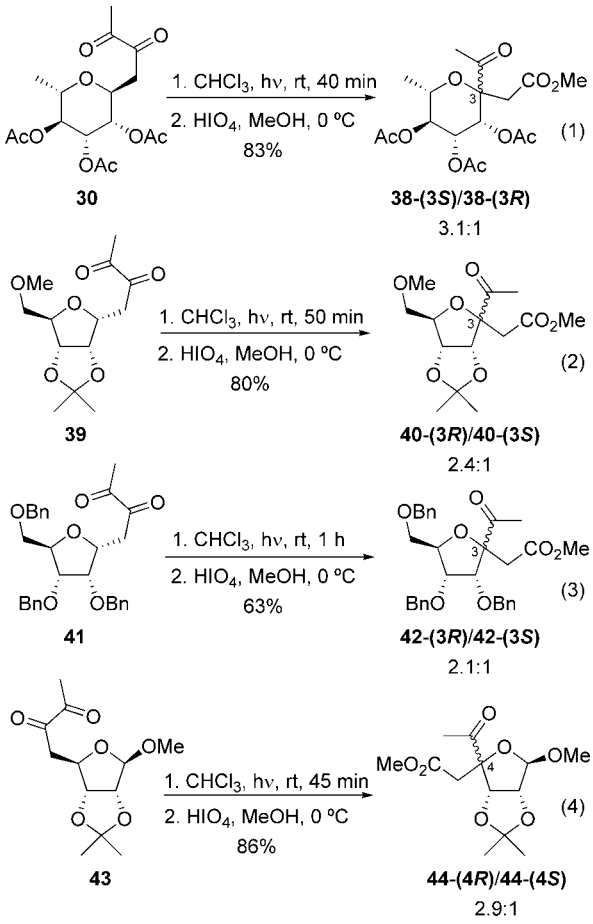
[a] SL: sunlight, UV: UV-lamp. [b] The ratios and stereochemistries were determined by ^{1}H NMR of the reaction crudes and NOESY experiments, respectively. For clarity, only the underlined diastereomers are depicted. [c] Yields refer to purified products. [d] Another two isomers with undefined stereochemistry were obtained with the ratio [**25-(2S)**/two isomers, 4:1.5:1]. [e] 0.4 M Naphthalene, 10 mM substrate.

ring moiety influenced by its substituents and stereoelectronic effects within the lifetime of this intermediate before the ISC occurs. In this case, four main favorable factors can play a major role leading to the product with retention at C5: Stabilizing interaction of the SOMO-C5 radical with the lone pair at the ring oxygen (pseudoanomeric effect) and the σ*-LUMO of the C6−O bond (β-oxygen effect) leading both to an axial C2−C5 bond formation via an early transition state,[27] the classical anomeric effect restricting the relative conformation between endocyclic oxygen and C9 and the possible existence of an intramolecular hydrogen bond C2−OH···O(Bn)−C6 favoring their *syn* approximation. Moreover, steric hindrance and/or the possible hydrogen bond formation C2−OH···O(Bn)−C6 probably enhanced the high stereocontrol at C2 of the product, because the introduction of a protic solvent led to a mixture of diastereomers (Table 1, entry 4).[26]

Compound **8**, dissolved in chloroform, was irradiated alternatively with sunlight, a UV lamp, or 3 daylight lamps affording products **14-(2*S*)** and **15-(2*R*)** with equal ratio and slightly different reaction times and yields (Table 1, entries 5–7). This scarce influence on yields and isomeric ratio of products, regarding the light source and the use of benzene instead of chloroform, was observed for all of the assayed models; therefore, the irradiation with UV light and chloroform as solvent were chosen to be the standard conditions to compare the results for each model. Although the ^{1}H NMR spectrum of the reaction crude showed a clean conversion into the two desired products, the reaction yield after purification was diminished in relation to model **4**, from which it differs only in the absence of the oxygenated substitution at C6 (Table 1, entries 3 and 6). The same feature was observed for models **19** and **24** in relation to **16** and **11**, respectively (compare entries 9 and 12, Table 1 and entries 1 and 2, Table 2). The main reason was the reduced stability of their corresponding cyclic products during the chromatographic purification on silica gel. The cyclization of model **8** occurred with 70% of retention at C5 and the stereochemistry at C2 of the spiro-product **14-(2*S*)** is the opposite of the observed for product **12-(1*R*)**, indicating an important contribution of the oxygenated substituent at C6 in the stereocontrol of the process. Interestingly, analysis of the spectroscopic data reveals that the pyranose ring of products **14-(2*S*)** and **15-(2*R*)** adopts the $^1C_4$ and $^4C_1$ conformation respectively, placing the C2 in equatorial position and directing the hydroxyl group toward the endocyclic oxygen, leading us to believed that a hypothetic hydrogen bond and/or the diminished steric shield at the 1,4-diradical intermediate **II-6** may play an important role in the stereocontrol at this asymmetric center (Figure 1). In fact, in an experiment not shown in Table 1, a mixture of the four possible stereoisomers of cyclic products is obtained if the reaction is carried out in the presence of a protic solvent (*tert*-butanol) in a ratio that is difficult to estimate due to the complexity of the ^{1}H NMR spectrum of the reaction crude.

(27) (a) Beckwith, A. L. J.; Duggan, P. J. *Tetrahedron* **1998**, *54*, 4623. (b) Beckwith, A. L. J.; Duggan, P. J. *Tetrahedron* **1998**, *54*, 6919.

SCHEME 6. Cyclization–Oxidative Opening Tandem Reaction[a]



[a] 1,3-Acetyl transference in pyranose and furanose models.

Irradiation of model **16** with a UV-lamp gave the expected products in excellent yield, as a mixture of three diastereomers (Table 1, entry 9). The reaction proceeded predominantly with retention at C5 (95%) [**17-(2*R*)** and **17-(2*S*)**], although the inversion product **18-(2*R*)** was also isolated. In this case, substrate **16** is in a $^4C_1$ conformation, but the pyranosyl ring of the intermediate **II-11** (Scheme 1) is conformationally more flexible and distortions are more likely, and even more so when placing the OMe group in the axial position, because of the anomeric effect at C9. The favorable contribution of the classical anomeric effect at C9 to the retention products at C5 seems to be less than the β-oxygen effect (compare entries 3, 6 and 9, Table 1).

The photoreaction of **16** in the presence of the triplet sensitizer benzophenone led almost to the same ratio of diastereomers (compare entries 9 and 10, Table 1). The reaction was complete in half-time, though the yield slightly decreased. In contrast, in the presence of pyrene, not only as a triplet quencher but also as a singlet sensitizer, the retention product **17-(2*R*)** was obtained with absolute diastereoselectivity and in high yield, although a longer reaction time was required (Table 1, entry 11). The cyclization of the singlet diradical **II-16** (S_1-spinisomer) intermediate is obviously so fast that rotations around the C4–C5 single bond do not take place. The configuration of the asymmetric center C2 in this last experiment is probably controlled by the existence of an intramolecular hydrogen bond, steric factors, and restricted rotation of C2–C3 in the short-lived singlet diradical **II-16** intermediate.

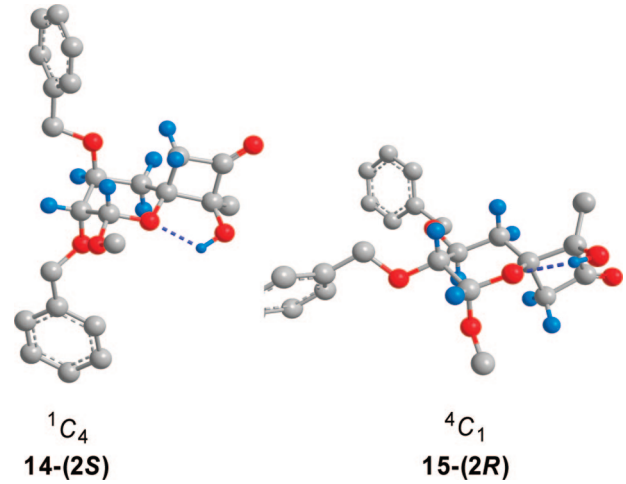


FIGURE 1. Molecular models of **14-(2*S*)** and **15-(2*R*)** obtained using CS Chem3D Pro v10.0 software. Benzyl and methyl hydrogens have been omitted for clarity.

It is important to mention that benzophenone, as triplet sensitizer, and pyrene and naphthalene, as triplet quenchers, have been assayed with all the substrates of Tables 1−2 with the aim of modulating the stereoselectivity. Indeed, despite model **16**, pyrene strongly inhibits the process, extending reaction times beyond 48 h and leading to the formation of contaminating side products, but scant influence on the stereoselectivity was observed for all other models. On the other hand, performing the photochemical reactions in the presence of naphthalene extended reaction times by 3.5–5 longer times but did not affect notably either the diastereomeric ratios or reaction yields as exemplified in entries 8 (Table 1) and 5 (Table 2). The presence of benzophenone significantly reduced reaction times to approximately 30–50%, but no considerable changes were observed in the stereoisomeric ratios. These experiments suggest an excited triplet state, but the high efficiency of pyrene in the stereocontrol of model **16** remains unclear at the present.

The possible stereoelectronic and conformational stability established by the presence of the oxygenated substitution at C6 and the axial position of the methoxyl group at the anomeric position is not present in model **19**. As may be expected, compound **19** cyclized with a lower percentage of retention at C5, the inversion product **21-(2*R*)** being the major one (Table 1, entry 12). The discussion about the stereocontrol observed at C2 for products **14-(2*S*)** and **15-(2*R*)** can be extended to products **20-(2*S*)** and **21-(2*R*)**.

Photocyclization of the *C*-glycoside **11** afforded the four possible stereoisomers in good yield (67% retention, Table 2, entry 1). A ^{1}H NMR experiment indicated that starting compound **11** adopts a $^4C_1$ conformation with the transferring hydrogen atom in the equatorial position. For this case, pseudoanomeric and β-oxygen effects play a disfavored contribution to obtain the retention products triggering conformational distortions to favor the axial reactivity of the generated transient radical at C5, explaining the low retention percentage. This reaction can be performed in a very efficient and environmentally friendly way, as shown in entry 2 of Table 2.

Upon irradiation under standard conditions, model **24** yielded three stereoisomers of cyclic products in a ratio of 4:1.5:1 (Table 2, entry 3). The major product was the isomer **25-(2*S*)**, but the stereochemistry of the other two minor stereoisomers could not be elucidated. Oxidative opening of the cyclobutanol moiety

of the mixture of the two nondetermined diastereomers (1.4:1) afforded product **35** (Scheme 5) and its epimer at C3 in a ratio of 1.1:1 respectively in a 56% yield, indicating that one of the undetermined isomers corresponded to **25-(2*R*)**. The absence of the oxygenated substituent at C6 in **11**, as in the case of 1,2-diketone **24**, enhanced the percentage of retention product from 67 to over 77% (compare entries 1 and 3, Table 2), showing the disfavored contribution of this substituent to the retention.

The experiments described in entries 4 and 6 demonstrate that the election of a different protecting group may be essential for the outcome of the reaction. Models **27** and **30** adopt a $^4C_1$ and $^1C_4$ conformation, respectively.[28] The photoreaction of model **27** involved transfer of a hydrogen atom in an axial position, affording exclusively the retention products. However, model **30**, which involved the transfer of an equatorial hydrogen atom, afforded the four possible isomers with 74% of retention. These examples indicate that conformational and/or steric shielding factors can play an important role for the stereocontrol of the process especially related to the asymmetric center C5 of the cyclic products. Model **30** achieved a clean cyclization and not spin center shift (SCS), resulting in a possible migration of the vicinal acetyl group to the pseudoanomeric position, was observed.[2f]

The 1-hydroxy-1-methyl-cyclobutan-2-one moiety could be opened with oxidative conditions using periodic acid in methanol in a preparative manner in excellent yield as depicted in Scheme 4.[3d] A diastereomeric mixture of compound **28-(2*S*)** and **28-(2*R*)** led to a single product **33**, which after deprotection afforded a new *C*-ketoside **34**. This procedure introduces a new entry into *C*-ketosides that can only be accessed through chemical synthesis.[29] Alternatively, this oxidative opening reaction can be achieved by treatment with *m*-chloroperbenzoic acid in dichloromethane followed by esterification with diazomethane in diethyl ether but is less efficient than the previously described procedure for all the assayed α-diketone models **8**, **19**, **27**, **39**, and **41**.[30]

Moreover, these oxidative opening conditions have been applied with good yields to the greater part of the studied models, whereas a lower efficiency was observed when benzyl protecting groups were present in the molecule. This is the case for all the examples shown in Scheme 5, where products **35**, **36**, and **37** were obtained in moderate yields (63, 61, and 50%, respectively), because partial oxidation and subsequent hydrolysis of the benzyl moiety, to afford more polar products, also occurs. This reaction was very useful to determine or verify the configuration of C5 in the cyclic products, especially valuable with isomeric irresolvable mixtures as shown in eqs 2 and 3 of Scheme 5.

The two-step conversion of 1,2-diketone derivatives into γ-ketoesters, as shown in Scheme 6, can be considered to be a stereocontrolled 1,3-transfer of the acetyl group. This methodology can be also extended to furanosyl derivatives. In most cases, this tandem cyclization-oxidative opening reaction should be preferentially addressed without purification of the cyclic intermediates especially those for which the spiro intermediates prove to be unstable during purification on silica gel. This was the case for all the furanose models assessed (**39**, **41**, and **43**). Any attempt of isolation of their spiro intermediate resulted in a considerably lower yield than the direct isolation of the final γ-ketoester. The Norrish-Yang photocyclization products derived from models **39** and **43** were isolated in 56 and 67% yield, respectively, whereas γ-ketoesters **40** and **44** were obtained in 80 and 86% yield with the tandem two-step procedure. The spiro compound derived from model **41** proved to be remarkably unstable at room temperature, decomposing over 50% within 24 h of isolation, despite being stored under nitrogen, whereas the isolated mixture of γ-ketoesters **42-(3*R*)** and **42-(3*S*)** (2.1:1) remained stable for over two weeks under air.

The results disclosed in Scheme 6 indicate that the Norrish-Yang reaction for all the furanose models, either *C*- or *O*-glycosides, proceeded predominantly with retention. The overall retention percentages, measured in the reaction crude by ^{1}H NMR, were 72, 68, and 73%, respectively, for models **39**, **41**, and **43**, which do not vary considerably with the ratios of the isolated products shown in Scheme 6. Analysis of the ^{1}H NMR of the crude of the photocyclization reaction with models **39** and **43** showed the formation of three stereoisomers for each one, with ratios (4.9:1.4:1) and (1.8:1.3:1), respectively. However, NOESY experiments were not conclusive for the assignment of the absolute configuration for any of the spiro products.

Scarce variations in yields, reaction times, and stereoisomeric ratios of products were observed upon irradiation with sunlight or daylight lamps instead of an UV lamp in this cyclization-oxidative opening tandem reaction, either with pyranose or furanose models. Glyconate derivatives **35**, **36**, **37**, **38**, **40**, **42**, and **44** are sugar-fused γ-ketoesters susceptible to further modifications to engineer versatile scaffolds and building blocks.

Conclusion

The results described herein demonstrate that the Norrish-Yang photocyclization of 1,2-diketones is well suited for the stereocontrolled synthesis of cyclobutanols fused to carbohydrate. The stereocontrol of the photocyclization is dependent on stereochemistries, functional groups, and ring-size of the precursors, and the results engage with the assumption of similar features between anomeric and pseudoanomeric radicals despite the respective lifetime. A tandem photocyclization-oxidative opening protocol proved to be very useful to prepare sugar-fused γ-ketoesters derived either from *O*- and *C*-glycosides or from pyranose and furanose models. This tandem protocol results in an efficient stereocontrolled 1,3-acetyl group transfer methodology.

These previous results appear promising in expanding the scope of this Norrish-Yang reaction with 1,2-diketones in asymmetric synthesis in the same way as arylketones or α-keto esters have already been used.[2] Further studies of this reaction, applied to noncarbohydrate derivatives as well as noncyclic chiral compounds, are currently underway in our laboratory.

Experimental Section

General Procedure for the Photocyclization of 1,2-Diketones. The corresponding 1,2-diketone was placed in a Pyrex glass vessel

(28) TBS protecting groups of pyranoses causes a flip of their conformation leading to $^1C_4$-form. Due to this conformational mobility, the L-rhamnose TBS derivatives prepared in this work exhibit broadened signals in their ^{1}H and ^{13}C NMR spectra at room temperature. (a) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663. (b) Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 5527. (c) Shuto, S.; Terauchi, T.; Yahiro, Y.; Abe, H.; Ichikawa, S.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 4151.

(29) See a list of procedures to generate *C*-ketosides: Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 1141.

(30) (a) Kedar, T. E.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 6121. (b) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 684.

with or without the indicated deoxygenated solvent (approximately 0.055 M). The vessel was purged with argon before being sealed and irradiated with sunlight, an UV lamp at 10 cm, or three daylight lamps at 7 cm until the reaction turned colorless. Concentration under vacuum, if required, afforded a residue that was purified by column or Chromatotron chromatography (hexanes–EtOAc mixtures) to give the spiro compounds. Specific conditions and yields are shown in Tables 1−2 and Scheme 6.

General Procedure for the Photocyclization of 1,2-Diketones with a Photosensitizers or Quencher. The corresponding 1,2-diketone (0.038 mmol) and photosensitizer (benzophenone) or quencher (pyrene, naphthalene) (0.5 mmol) was dissolved in $CDCl_3$ (1 mL), placed in a 5-mm NMR tube, which was purged with argon before being closed. The reaction mixture was irradiated with a UV–lamp at 10 cm until complete conversion and the solvent was removed under vacuum. The reaction was monitored by ^{1}H NMR. Chromatotron chromatography of the residue with (hexanes) to remove the photosensitizer followed by (hexanes-EtOAc mixtures) afforded the cyclic compounds.

General Procedure for the Tandem Photocyclization–Oxidative Opening Reaction from 1,2-Diketones. Following the general procedure of photocyclization with deoxygenated $CHCl_3$ as solvent and irradiation with an UV lamp for approximately 1 h, the corresponding 1,2-diketones (1 mmol) afforded the cyclic compound usually as a mixture of various stereoisomers. After the solvent was removed under vacuum, HIO_4 (3.5 mmol) was added to the solution of this residue in MeOH (30 mL) at 0 °C and stirred for 1 h at this temperature followed by another hour at rt. The reaction mixture was quenched with saturated solution of Na_2CO_3 and extracted 3 times with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuum. The ^{1}H NMR of the residue showed the ratio of the two possible stereoisomers. Chromatotron chromatography (hexanes-EtOAc mixtures) of the residue afforded the sugar-fused γ-ketoesters.

Acknowledgment. This work was supported by the research programs Nos. CTQ2004-06381/BQU and CTQ2004-02367/BQU of the Ministerio de Educación y Ciencia, Spain, cofinanced by the Fondo Europeo de Desarrollo Regional (FEDER). A.J.H. and M.R. thank the Program I3P-CSIC and ULA-Venezuela, respectively, for a research contract.

Supporting Information Available: General and chemical information plus experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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