JOC*Note*

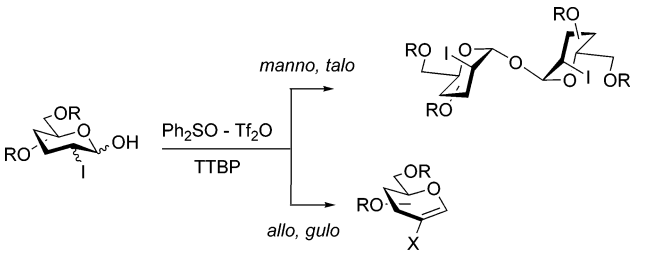
Synthesis of 2-Iodoglycals, Glycals, and 1,1′-Disaccharides from 2-Deoxy-2-iodopyranoses under Dehydrative Glycosylation Conditions

Miguel Angel Rodríguez,[†] Omar Boutureira,[†] M. Isabel Matheu,[†] Yolanda Díaz,*[,†] Sergio Castillón,*[,†] and Peter H. Seeberger[‡]

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel·lí Domingo s/n, 43007 Tarragona, Spain, and Laboratorium für Organische Chemie, Swiss Federal Institute of Technology, ETH Zürich, HCI F315, Wolfgang-Pauli Strasse 10, 8093 Zürich, Switzerland

sergio.castillon@urv.cat; yolanda.diaz@urv.cat

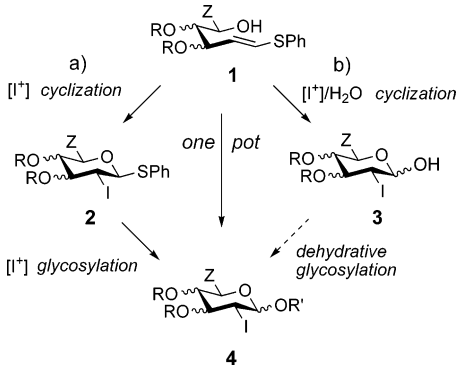
Received August 7, 2007



Treatment of 2-deoxy-2-iodopyranoses under dehydrative glycosylation conditions afforded pyranose glycals, 2-iodoglycals, and 1,1′-disaccharides instead of the expected glycoside products. While the product distribution revealed that this reaction is very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodopyranoid glycals can be obtained almost exclusively in good yields by employing 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group. The behavior of 2-deoxy-2-iodopyranoses during the dehydrative elimination reaction has been analyzed in detail.

Dehydrative glycosylation is an efficient glycosylation procedure that uses 1-hydroxysugars as glycosylating agents and diphenyl sulfoxide and triflic anhydride as activators to produce glycosides and disaccharides in good yields. These glycosylations proceed via an oxosulfonium intermediate that may evolve to an oxocarbenium ion with concomitant regeneration of diphenyl sulfoxide. The nucleophilic acceptor subsequently adds to the anomeric center to yield the desired glycosylated product in a *one-pot* procedure. Activated or deactivated glycosyl donors react equally well, and the procedure also allows for the *N*-glycosylation of amides.[1] This methodology includes iterative,[2] orthogonal,[3] 1,2-*cis*,[4] and catalytic activated[5] glycosylations, but generally, preactivation of the glycosylating agent is required prior to addition of the acceptor.[6]

SCHEME 1. Glycosylation Procedures from Alkenyl Sulfanyl Derivatives 1



Recently, we reported the synthesis of 2-deoxy-2-iodohexopyranosyl thioglycosides **2** that are efficient glycosylating agents for the stereoselective synthesis of 2-deoxy-2-iodoglycosides and oligosaccharides **4**. The key step in the synthesis of these donors was the cyclization of alkenyl sulfanyl derivatives **1** with iodonium reagents (Scheme 1, path a).[7] The reaction time and temperature had to be carefully controlled. Forcing reaction conditions to ensure full conversion usually resulted in the activation of the already formed thioglycoside **2**. Thus, variable amounts of the corresponding 2-iodolactol **3** were recovered usually after workup in unoptimized experiments with labile substrates. The reaction can be also performed in *one-pot* fashion from the sulfanyl alkene **1** by cyclization and in situ activation of the thioglycoside in the presence of the corresponding alcohol.[8] This procedure avoids the formation of the 2-iodolactols.

We considered that the corresponding 2-iodolactols **3** could be directly obtained when performing the cyclization reaction in the presence of small amounts of water. 2-Iodolactols could be used for the dehydrative glycosylation procedure (Scheme 1, path b), in order to expand the synthetic scope of the 2-iodo derivatives and provide the basis for orthogonal glycosylation procedures.[3] Initially, phenylsulfanylalkene **5** was reacted with NIS in wet CH_3CN to access 2,6-dideoxy-2-iodopyranose **6**, a precursor in the synthesis of oligosaccharides present in natural products such as digitoxine. Compound **6** was treated with Tf_2O, Ph_2SO, and 2,4,6-tri-*tert*-butylpyrimidine (TTBP) in CH_2Cl_2 at −60 °C. Surprisingly, the product was partially transformed

[†] Universitat Rovira i Virgili.
[‡] Swiss Federal Institute of Technology.

(1) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. (c) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766.

(2) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414.

(3) Codeé, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947.

(4) Codeé, J. D. C.; Hossain, L. H.; Seeberger, P. H. *Org. Lett.* **2005**, *7*, 3251.

(5) (a) Boebel, T. A.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 5874. (b) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818.

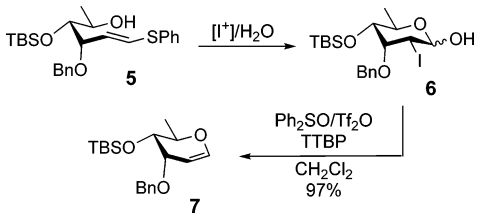
(6) Codeé, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057.

(7) (a) Arnés, X.; Díaz, Y.; Castillón, S. *Synlett* **2003**, 2143. (b) Rodríguez, M. A.; Boutureira, O.; Arnés, X.; Matheu, M. I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297. (c) Kövér, A.; Matheu, M. I.; Diaz, Y.; Castillón, S. *Arkivoc* **2007**, 364.

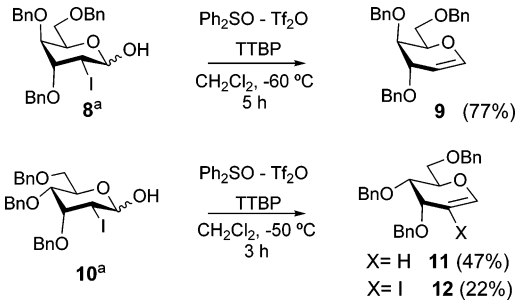
(8) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 2470.

10.1021/jo701738m CCC: $37.00
Published on Web 10/11/2007

SCHEME 2. Dehydrative Elimination Reaction in 2,6-Dideoxy-2-iodopyranoses



SCHEME 3. Synthesis of Glycals by Dehydrative Elimination[a]



[a] 2-Deoxy-2-iodopyranoses synthesized from the corresponding phenylsulfanyl alkenes.

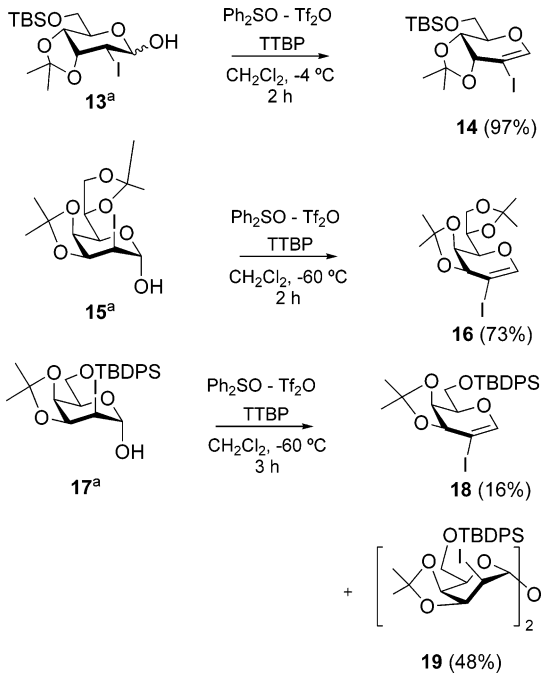
within a few minutes into a new compound, even before adding a nucleophile. Glycal **7** was obtained in excellent yield after 1 h (Scheme 2). To avoid this elimination, lower temperatures (−80 to −100 °C), less base (1 to 3 equiv of TTBP), and different dehydrative promoters (BSP,[9] alkyl sulfides) were tested, but all yielded the same glycal.

We recently demonstrated that glycals can be easily and efficiently obtained by treating 2-deoxy-2-iodo-1-thioglycosides **2** under reductive-elimination conditions.[10] However, glycal **7** must be formed via a completely different mechanism. To elucidate the reaction mechanism we prepared a set of 2-deoxy-2-iodo-pyranoses with *gulo*-**8**, *allo*-**10**, **13**, *talo*-**15**, **17**, **22**, and *manno*-**20** configuration by treating the corresponding phenyl sulfanyl alkenes[7b] (or glycals) with NIS in wet CH_3CN.

Thus, 2-iodolactols **8** and **10** were subjected to dehydrative conditions to afford the corresponding glycals **9** and **11** (Scheme 3). In the case of ribo derivative **10**, 2-iodoglycal **12** was obtained in minor amounts (22% yield). In order to confirm that glycal **11** was not derived from 2-iodoglycal **12**, following isolation, **12** was submitted to dehydrative elimination conditions. Recovery of iodoglycal **12** indicated that it was formed in a irreversible way.

Interestingly, isopropylidene-protected iodolactols **13** and **15** rendered exclusively the 2-iodoglycals **14** and **16** in good to excellent yield (Scheme 4). In the case of 2-deoxy-2-iodopyranose **17**, minor amounts of 2-iodoglycal **18** were also obtained, together with 1,1′-disaccharide **19**. The presence of the isoproylidene group is crucial for obtaining 2-iodoglycals in good yield as can be deduced by comparing the configurationally identical compounds **10** and **13**. A singlet at ∼6.8 ppm assigned to H1 in the ^{1}H NMR spectra, and two signals at ∼148 ppm

SCHEME 4. Synthesis of 2-Iodoglycals by Dehydrative Elimination[a]



[a] 2-Deoxy-2-iodopyranose synthesized from the corresponding phenylsulfanyl alkenes.

and ∼75 ppm assigned to C1 and C2, respectively, in the ^{13}C NMR spectra indicated the formation of the 2-iodo-substituted double bond.

Glycals and 2-iodoglycals are versatile synthetic intermediates. Insertion of substituents in C1 structures by deprotonation (*C*-glycosides, quinones)[11] or introduction of C2 vinyl substituents by Heck-type reaction[12] yield iso-*C*-glycosides. Iodine is preferable over chlorine or bromine for these reactions.[13] However, only one synthesis dealing with 2-iodoglycals has been disclosed to date.[14]

Manno-**20** and *talo*-**22** derivatives were reacted under the same conditions to give 1,1′-disaccharides **21** and **23**, respectively, resulting from the self-condensation of the starting 2-iodolactols (Scheme 5).

The conversion of compound **I** to **III** (Scheme 6) represents an overall base-assisted hydroxyl elimination process[15] that might be occurring through the initial 1-OH activation followed by elimination of Ph_2SO and tri-*tert*-butylpyrimidinium triflate (TTBPHOTf) to render 2-iodoglycal **III**. Similarly, the production of **IV** might be explicable in terms of nitrogen assisted iodine elimination in **II** to afford the corresponding glycal[16] (Scheme 6). Further credence to this hypothesis is provided by the fact that only *N*-containing bases[17] such as TTBP, or

(9) For the use of benzensulfinylpiperidine (BSP) in glycosylation, see: (a) Crich, D.; Smith, M. J. Am. Chem. Soc. **2001**, *123*, 9015. (b) Crich, D.; Li, H. *J. Org. Chem.* **2001**, *67*, 4640.

(10) Boutureira, O.; Rodríguez, M. A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673.

(11) Hallett, M. R.; Painter, J. E.; Quayle, P.; Ricketts, D.; Patel, P. *Tetrahedron Lett.* **1998**, *39*, 2851.

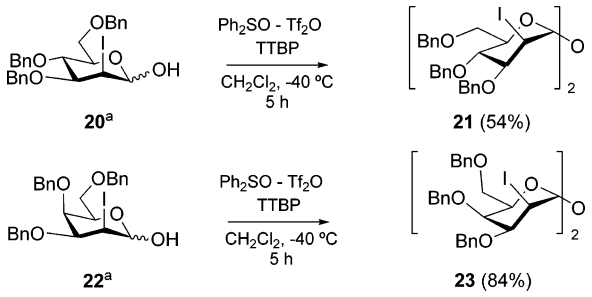
(12) (a) Gómez, A. M.; Danelón, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002**, 2024. (b) Gómez, A. M.; Pedregosa, A.; Barrio, A.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2004**, *45*, 6307.

(13) (a) R. F. Heck, *Acc. Chem. Res.*, **1979**, *12*, 146. (b) Turner, W. R; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 281.

(14) Chemier, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949.

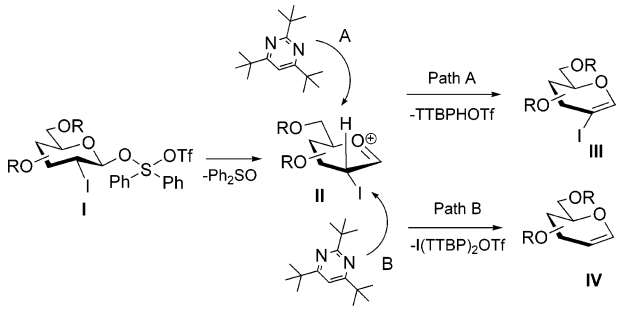
(15) For a similar outcome in exo-glycals with IDCP as a base, see: Noort, D.; Veeneman, G. H.; Boons, G.-J. P. H.; Van der Marel, G. A.; Mulder, G. J. van Boom, J. H. *Synlett* **1990**, 205.

SCHEME 5. Synthesis of 1,1′-Disaccharides by Dehydrative Elimination[a]



[a] 2-Deoxy-2-iodopyranose synthesized from the corresponding phenylsulfanyl alkenes.

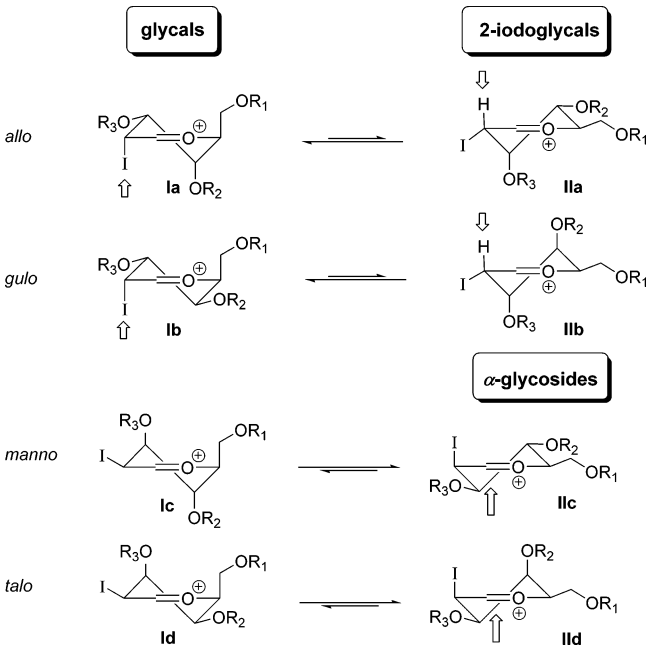
SCHEME 6. Plausible Mechanism for Product Distribution during Dehydrative Elimination of 2-Deoxy-2-iodopyranoses



phosphazene P_4-*t*-Bu, that are able to stabilize [I^+] species afforded glycals, while *t*-BuOK failed and no reaction products were detected.

According to these results, the chairlike oxocarbenium intermediates **Ia**−**d** and **IIa**−**d** (Scheme 7) play an important role for the chemoselectivity of dehydrative elimination reactions. Moreover, intermediates **Ia**,**b** (allo and gulo) and **IIc**,**d** (manno and talo) that contain axial iodine are likely to be more stable than the corresponding equatorial iodine conformers due to stabilizing hyperconjugative interactions between σC−I and π*C−O of the oxocarbenium.[18] Furthermore, during the E1 elimination reaction, the new double bond can only form when the vacant p orbital of the carbocation and the breaking C−H or C−I bond are aligned in parallel. Therefore, the group to be eliminated must be in the axial position. Consistent with this view, dehydrative elimination of the gulo-configured 2-deoxy-2-iodopyranose **8** proceeded through the more stable conformer Ib and elimination of the axial iodide provided glycal **9** in excellent yield. Similarly, axial iodine elimination of allo-configured 2-deoxy-2-iodopyranose **6** in the more stable conformation **Ia** rendered exclusively glycal **7**. In this case, the equilibrium between conformers is considerably shifted toward Ia due to destabilizing gauche effects between the TBS[19] group

SCHEME 7. Stereochemical Courses of Dehydrative Elimination of 2-Deoxy-2-iodopyranoses



(OR_2) and the C-6 substituent (OR_1) in conformer **IIa**. In the case of tri-*O*-benzyl-protected allo-configured 2-deoxy-2-iodopyranose **10**, the elimination mainly proceeded through the more stable intermediate Ia to render glycal **11**. However, a minor amount of conformer IIa also reacted to give 2-iodoglycal **12**.

Dehydrative glycosylation of 2-deoxy-2-iodo-pyranoses of manno (**20**) and talo (**22**) configurations afforded the 1,1′-disaccharides **21** and **23**, respectively, as single α-anomers. In this case, self-condensation of the 2-deoxy-2-iodopyranoses from the more stable conformer **IIc**,**d** is faster than elimination.

Particularly, allo- and gulo-configured glycosylating agents afforded only glycals and 2-iodoglycals, while manno and talo sugars yielded disaccharides. This finding can be explained by the presence of steric interactions between the C-6 substituent (OR_1) and the incoming nucleophile in the most stable conformer **Ia,b** (allo and gulo) when compared with **IIc,d** (manno and talo), where such destabilizing interactions do not exist (Scheme 7). These findings highlight the critical role the 2-deoxy-2-iodopyranose configuration exerts on this new dehydrative elimination process.

Finally, in order to rationalize the observed chemoselectiviy of the 2-deoxy-2-iodopyranoses bearing a 3,4-*O*-isopropylidene protecting group, we considered that the reaction might operate by way of a constrained conformation[20] such as **III** and **IV**, upon which highly favored proton elimination may occur instead of the opposite iodine abstraction (Figure 1).[21]

In summary, despite the fact that dehydrative glycosylation has proved to be an efficient and general glycosylation method, its application to 2-deoxy-2-iodopyranoses did not always afford the expected products. The treatment of 2-deoxy-2-iodopyra-

(16) Stabilization/elimination of [I^+] by the nitrogen atom has been reported previously: (a) Mongin, F.; Rebstock, A.-S.; Trécourt, F.; Quéguiner, G.; Marsais, F. *J. Org. Chem.* **2004**, *69*, 6766. (b) Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, *66*, 4304. (c) Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, *55*, 3104.

(17) A similar behavior was observed with DBU; see: Álvarez de Cienfuegos, L.; Mota, A. J.; Robles, R. *Org. Lett.* **2005**, *7*, 2161.

(18) Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.

(19) (a) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (c) Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 1576.

(20) For a review dealing with the use of cyclic bifunctional protecting groups, see: Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2007**, *342*, 419.

(21) A similar behavior was observed in the selenium induced cylization of 3,4-*O*-isopropylidene-protected alkenyl sulfides: Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón S. *Eur. J. Org. Chem.* **2007**, 3564.

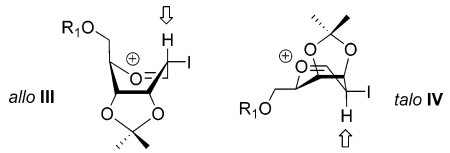


FIGURE 1. Stereochemical features in dehydrative eliminations of activated 2-iodolactols.

noses using dehydrative glycosylation conditions afford glycals, 2-iodoglycals, and self-condensation disaccharides depending on the configuration of the starting 2-deoxy-2-iodopyranoses and the protecting groups. Thus, allo- and gulo-configured compounds afforded glycals, while manno and talo derivatives gave glycosylated products. Moreover, 2-iodopyranose glycals can be obtained in mostly good yield by employing 3,4-*O*-isopropylidene protecting groups. A detailed analysis of the fate of 2-deoxy-2-iodopyranoses during dehydrative glycosylations provided insight into the mechanism of this process.

Experimental Section

General Procedure for Dehydrative Elimination from 2-Iodopyranoses. A mixture of the 2-iodolactol product (1.0 mmol), prepared by treating sulfanyl alkenes or glycals with NIS−water in acetonitrile, Ph_2SO (2.0 mmol), and TTBP (3.0 mmol) in CH_2Cl_2 (0.04 M to iodolactol) were stirred over flame-dried molecular sieves for 30 min, after which the reaction mixture was cooled to −60 °C. Tf_2O (1.0 mmol) was added, and the mixture was first brought to −40 °C and then slowly warmed to the completion of the reaction (TLC). The reaction was quenched by the addition of Et_3N (10 mmol) and concentrated in vacuo. The crude product was purified by chromatographic techniques.

Acknowledgment. We acknowledge the financial support of DGESIC, CTQ2005−03124 (Ministerio de Educación, Spain) and the ETH Zurich. We thank I. Cobo for preliminary studies and Servei de Recursos Científics (URV) for technical assistance. Fellowships from DURSI (Generalitat de Catalunya) and Fons Social Europeu to O.B. and M.A.R are also acknowledged.

Supporting Information Available: General experimental methods, experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701738M