Pergamon

Tetrahedron Letters, Vol. 35, No. 34, pp. 6263-6266, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01293-8

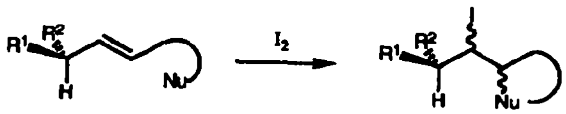
A Phenyl-assisted Asymmetric Iodolactonisation Reaction

Reinhard W. Hoffmann*, Rainer Stürmer, and Klaus Harms

Philipps-Universität Marburg
Fachbereich Chemie
D - 35032 Marburg, Germany

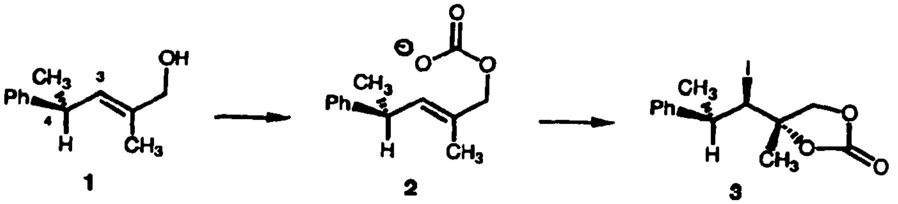
Abstract: *Iodo-lactonisation of the allylic carbonate **2** proceeded with high diastereoselectivity to give the iodocarbonate **3**. Iodine attacked the double bond in **2** from the face, which is flanked by the phenyl group. This suggests an activating effect of the phenyl group in this reaction.*

The iodo-lactonisation reaction is a valuable tool to create oxygen carrying stereocenters.[1] Asymmetric induction from a stereogenic center in the chain linking the carboxyl group to the prostereogenic double bond has been used quite widely. Much less studied are processes, in which asymmetric induction originates from a stereocenter at the "other" end of the reacting double bond. This has been termed "type C" by Chamberlin and Hehre in their comprehensive analysis of asymmetric iodo-lactonisation reactions.[2]

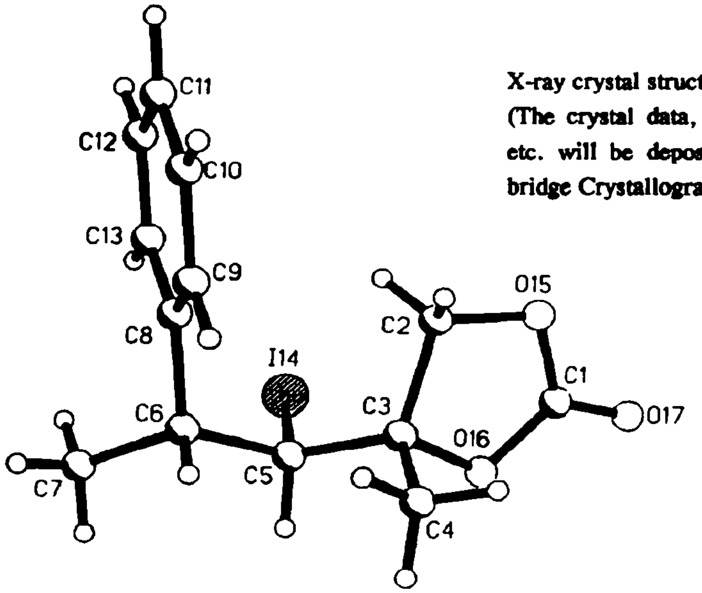


These authors provided the first example for such an iodo-lactonisation reaction, which, however, resulted in a low diastereoselectivity. The only related example, we are aware of, is a highly stereoselective mercuri-cyclisation carried out by D.A. Evans in the course of the synthesis of a polyether antibiotic.[3] We considered the formation of an iodocarbonate,[4] cf. 7 → 9, below, in the context of our erythronolide synthesis [5] as a means to set up the stereogenic center at C-6 of erythronolide. Before implementing this step into the erythronolide synthesis we carried out a model study, which is reported here.

We elected the allylic alcohol **1** for a study, because 1,3-allylic strain [6] should control the conformation around the C-3/C-4-bond linking the stereogenic center at C-4 to the prostereogenic double bond. In the derived carbonate **2** the phenyl group is placed over one face of the double bond and the methyl group over the other face.

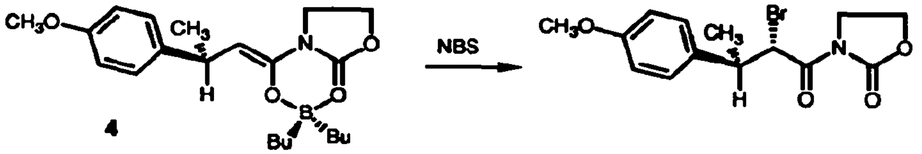


A solution of the lithium alkoxide 2 derived from 1 with butyllithium in THF was saturated with carbon dioxide at 0°C to give the carbonate 2. Treatment with iodine while maintaining a carbon dioxide atmosphere led to a slow (3d) conversion into a single iodo lactone 3. After purification by flash chromatography the crystalline 3 (m.p. 113°C) was isolated in 71% yield.[7] The relative configuration at the three stereogenic centers was determined by X-ray structure analysis of crystals grown from diisopropyl ether. The structure of 3 reveals that iodine had attacked the double bond in 2 from the side of the phenyl group.

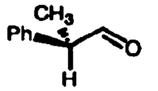


X-ray crystal structure of 3
(The crystal data, atomic coordinates, etc. will be deposited with the Cambridge Crystallographic Data Center)

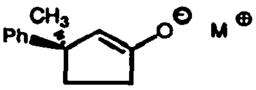
This result merits discussion, because the stereochemical course of the iodo-lactonisation of 2 is diametrically opposed to that of the reaction of 4 with NBS recently reported.[8] Steric as well as electronic effects have to be taken into consideration: While a phenyl group has a higher A-value then a methyl group,[9] there are indications that a phenyl group may behave as the smaller residue in aldol-additions with Z-enolates [10] or allylmetallation with Z-crotylboronates [11] of the aldehyde 5. Cuprate additions to the alkylidenemalonate derived from 5 showed variable stereoselectivity.[12] Moreover, bromination (Br$_2$, -78°C) of the enolate 6 has been reported to occur preferentially from the face carrying the phenyl group.[13]



4



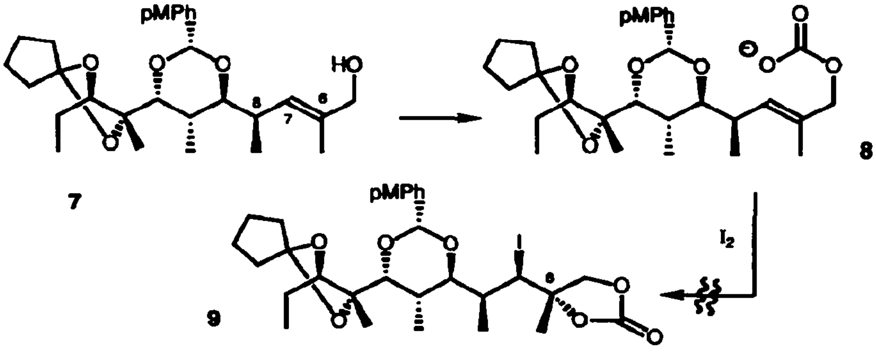
5



6

While the stereochemistry of the latter bromination reaction has been ascribed to coordination of the lithium cation to the phenyl group, a precoordination of bromine (in the case of 6) or iodine (in the case of 2) to the phenyl group could also be considered. This appears not unreasonable in view of the association constant for iodine with toluene of 0.2 to 0.5 $mol\ l^{-1}$, [14,15] that for bromine association should be even larger. The difference in the sense of asymmetric induction in the reactions of 2 with iodine on the one side and of 4 with NBS on the other would then have to be attributed to a precomplexation of iodine to the phenyl group in 2 and the absence of such precomplexation between the anisyl group and NBS in the case of 4, due to the lower polarizeability of NBS compared to that of iodine.

We then turned to the iodolactonisation reaction of the intermediate 8 in order to set up to the C-6 stereocenter in our erythronolide synthesis.[5] The conformation of the C-7/C-8 bond in 7 is again controlled by 1,3-allylic strain.[6] However, 7 contains no activating phenyl group at the allylic stereocenter. Differentiation of the two faces of the C-6/C-7 double bond would have to rely on steric effects alone: The small methyl group is on the top face and the bulky 1,3-dioxane shields the bottom face of the double bond. We were, however, unable to effect the desired iodo-carboxylation of 8 to 9 under the conditions used for the conversion of 1 into 3. Longer reaction times led to decomposition and acetal cleaveage [16] of 7. Given the fact, that the phenyl-assisted iodo-lactonisation of 2 is slow, the reaction of 8 which lacks such a phenyl group becomes too slow to be useful. If iodine complexes to the p-methoxyphenyl group or the 1,3-dioxane [15] in 8 this complexation is not productive toward the formation of 9.



7

8

9

Acknowledgements: We are grateful to the Deutsche Forschungsgemeinschaft and the Graduierten-Kolleg "Metallorganische Chemie" for support of this study.

References and Notes

1. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3-72; Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321-3408.
2. Chamberlin, A. R.; Mulholland, R. L.; jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672-677.
3. Bender, D. A. Evans S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.
4. Cardillo, C.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465-466; Haslanger, M. F.; Ahmed, S. *J. Org. Chem.* **1981**, *46*, 4808-4810; Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013-4018; Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626-4633.
5. Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem.* **1993**, *105*, 112-114; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101-103.
6. Johnson, F. *Chem. Rev.* **1968**, *68*, 375-413; Hoffmann, R. W. *Chem. Reviews* **1989**, *89*, 1841-1860.
7. **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, J = 6.9 Hz, 3 H), 1.71 (s, 3 H), 2.95 (quint., J = 6.9 Hz, 1 H), 3.88 and 3.93 (AB-system, J = 9.0 Hz, 2 H), 4.44 (d, J = 7.5 Hz, 1 H), 7.25 (m, 5 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 23.4, 43.6, 48.9, 77.2, 85.0, 127.59, 127.61, 128.5, 143.3, 153.8.
8. Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron Lett.* **1994**, *35*, 2301-2304; cf. also Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561-2564; Li, G.; Russell, K. C.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565-2568.
9. Hirsch, J. A. *Topics Stereochem.* **1967**, *1*, 199-222.
10. Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151-4157.
11. Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395-2401.
12. Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572-1573.
13. Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.
14. Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1952**, *74*, 4500-4503; Foster, R. in: Molecular Complexes; Foster, R., Ed.; Elek Science Publ.; London, 1974, Vol. 2, pp. 108-172.
15. Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1987**, *52*, 2690-2694.
16. Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827-3830.

(*Received in Germany* 16 *June* 1994; *accepted* 28 *June* 1994)