Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 6590–6593
Tetrahedron Letters

Conformational control of selectivity in the dienone–phenol rearrangement

Anne M. Sauer,[a] William E. Crowe,[a,*] Gregg Henderson[b] and Roger A. Laine[c]

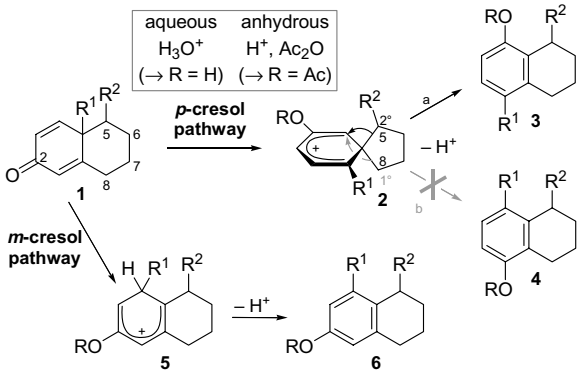
[a]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, United States
[b]Department of Entomology, Louisiana State University, Agricultural Center, Baton Rouge, LA 70803, United States
[c]Department of Biological Sciences, Louisiana State University, Baton Rouge, LA 70803, United States

Received 25 July 2006; revised 25 June 2007; accepted 2 July 2007
Available online 7 July 2007

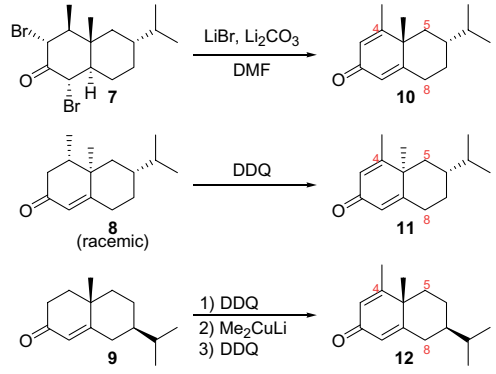
Abstract—We have explored the dienone–phenol rearrangement of substrates where: only the *p*-cresol pathway is possible and relative migratory aptitudes should play no role in determining the regiochemistry of the reaction. For these substrates the selectivity of the rearrangement was found to depend on the stereochemistry of the spirocyclic intermediate formed during the course of the rearrangement. Rearrangement of one of these substrates gave—surprisingly—a single regioisomeric product. Selectivity in this case can be correlated with the relative stability of cationic intermediates, which lie on the pathway between spirocycle and final product.

Dienone–phenol rearrangement (DPR) reactions, in which naphthalenic dienones of type **1** undergo isomerization to phenolic products upon treatment with acidic media, have been extensively studied.[1] A mixture of two phenols is generally obtained, which result from two separate pathways: 1,2-migration of the saturated ring (C_5) produces a spirocyclic intermediate **2**, which leads to **3** (*p*-cresol pathway); 1,2-migration of the bridgehead substituent (R^1) and subsequent deprotonation of intermediate **5** leads to **6** (*m*-cresol pathway). Competition between the two pathways has been shown to be influenced primarily by the relative migratory aptitudes of R^1 and C_5 but also by the media in which the reaction is run.[2] There are a number of cases where either *p*-cresol **3** or *m*-cresol **6** may be formed with high selectivity. Formation of the alternative the *p*-cresol product **4** is never a major pathway due to the lower migratory aptitude of the primary carbon (C_8) compared to the secondary carbon (C_5).

In conjunction with other studies involving the preparation and biological testing of eremophilane-type sesquiterpenes and simple derivatives, we had an occasion to examine the dienone–phenol rearrangement of the nootkatone-derived dienone **10** (Scheme 2). The unexpected selectivity of this reaction prompted us to examine the



Scheme 1. Naphthalenic DPR.



Scheme 2. Preparation of dienone substrates.

* Corresponding author. Tel.: +1 225 578 2060; fax: +1 225 578 3458; e-mail: wcrowe1@lsu.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.001

dienone–phenol rearrangements of isomeric compounds **11** and **12** (Scheme 2). Herein we report the results of these studies, which reveal hitherto unexplored conformational factors influencing the regiochemical course of the reaction.

Compound **10** was prepared by dehydrohalogenation of dibromide **7**, which we described previously.[3] Compounds **11** and **12** were prepared from known Robinson annulation products **8**[4] and **9**[5] (Scheme 2).

Compounds **10**–**12** differ from typical naphthalenic dienone–phenol substrates (Scheme 1) in two important respects. Due to the presence of a methyl group at C_4 (blocking deprotonation in the *m*-cresol pathway) only the *p*-cresol pathway is possible. Due to the lack of substitution on C_5 and C_8, the competing *p*-cresol pathways equally favorable in terms of migratory aptitude.

Treatment of **10** with acetic anhydride containing a drop of sulfuric acid produced, instead of the expected mixture of regioisomers **14** and **15**, a single phenol acetate product. The identity of this product, established by single crystal X-ray analysis, was shown to be **14** (Fig. 1). It appears that the isopropyl group at C_6 has a marked influence on the relative rate of C_5 versus C_8 migration in the spirocyclic intermediate **13** with preferential C_8 migration leading to the observed product (Scheme 3).

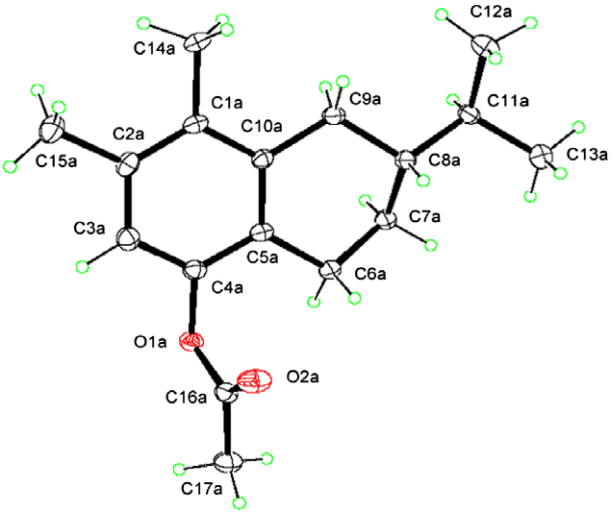
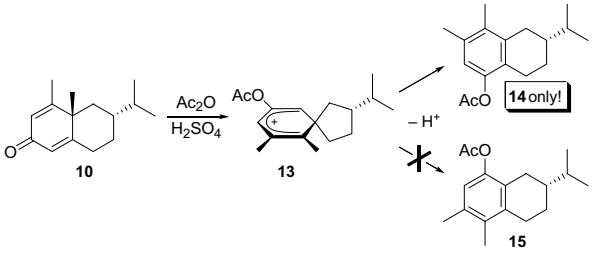
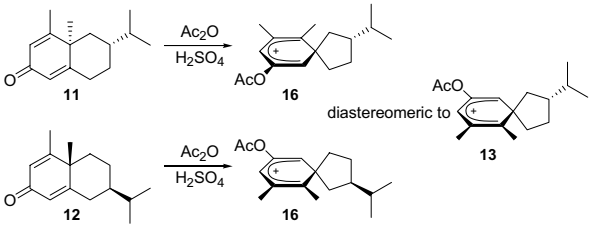


Figure 1. Crystal structure of **14**.



Scheme 3. DPR of **10**.

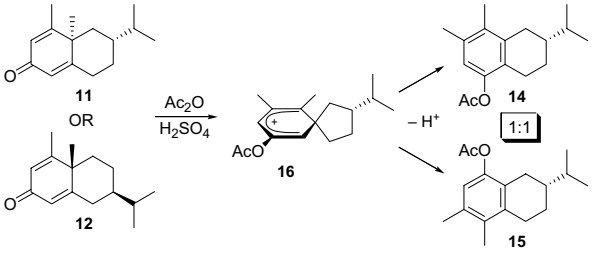


Scheme 4. Substrates **11** and **12** rearrange via a common spirocyclic intermediate.

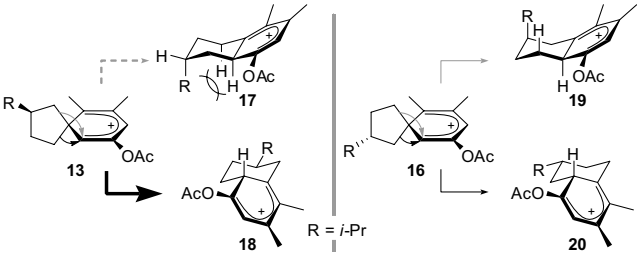
Dienone–phenol rearrangements of isomeric structures **11** and **12** were expected to favor the same product since they should proceed via a common spirocyclic intermediate **16** (Scheme 4). Since this spirocyclic intermediate is diastereomeric to **13**, formed in the rearrangement of **10**, we anticipated that these reactions would show a different product distribution.

Dienone–phenol rearrangements of substrates **11** and **12**, in contrast to the corresponding reaction of **10**, were found to be unselective (Scheme 5). Treatment of **11** or **12** with acetic anhydride containing a drop of sulfuric acid produced a 1:1 mixture of phenol acetates **14** and **15**.

Selectivity of the dienone–phenol rearrangements proceeding through the diastereomeric intermediates **13** and **16** roughly correlates with the relative stability of the cationic intermediates formed by competing C_5 versus C_8 migration (Scheme 6). The preferential formation of phenol acetate **14** from dienone **10** correlates with the greater stability of cationic intermediate **18** (converted to **14** by loss of a proton) from the spirocyclic intermediate **13**. Cation **18** possesses an equatorial isopropyl group whereas the competing intermediate **17** suffers from a pair of 1,3-diaxial interactions involving the



Scheme 5. DPR of **11** and **12**.



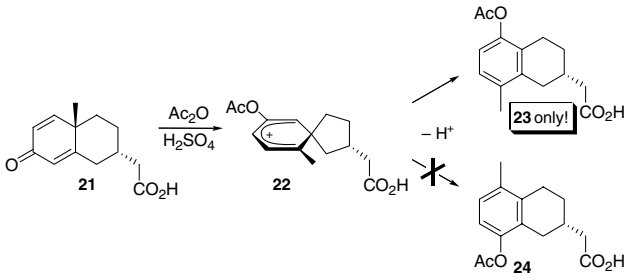
Scheme 6. Correlation between selectivity and stability.

isopropyl group. Based on this type of correlation, we expected rearrangement of dienones **11** and **12** to favor phenol acetate **15** since the cationic intermediate leading to this product (**20**) bears an equatorial isopropyl group while the competing pathway leading to **14** proceeds through an intermediate (**19**) bearing an axial isopropyl group. However, the rearrangements of **11** and **12** should be less selective than that of **10** since the less stable intermediate (**19**) suffers from only a single 1,3-diaxial interaction instead of a pair of such interactions.

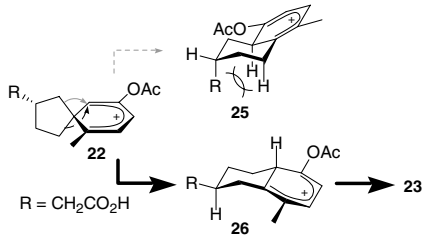
Discussion of DPR regiochemistry has focused on other factors such as differences in migratory aptitude or steric interactions resulting from substituents at C_5 or C_8. The correlation between the regiochemistry of the dienone–phenol rearrangement and the stereochemistry of the spirocyclic intermediate (e.g., **13** vs **16** as demonstrated above) has not previously been recognized. We suspect that stereochemistry, and concomitant conformational issues, may play an unrecognized role in determining the course of these reactions. In accordance with this suspicion, we note that in 1960 Hirakura reported that under anhydrous conditions, the dienone–phenol rearrangement of *trans*-dienoneacetic acid **21** provided the *p*-type cresol **23**, exclusively (Scheme 7).[6]

Through the examination of the stability of cationic intermediate **25**, one can see that this system suffers from a pair of destabilizing 1,3-diaxial interactions, like that of previous intermediate **17**. The alternative pathway, proceeding via reaction intermediate **26**, orients the carboxymethyl substituent in the more stable, equatorial position, thereby providing a favorable route to the exclusive production of the phenolic acetate **23** (Scheme 8).

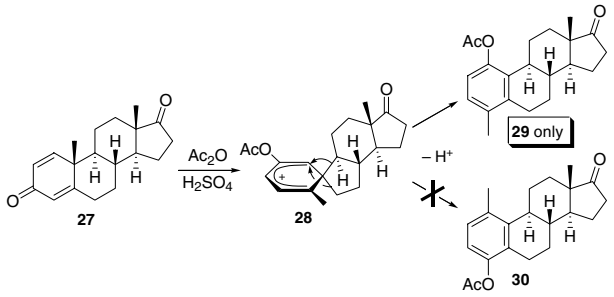
Steric issues such as those described in Schemes 6 and 8 seem to play an important role in determining DPR selectivity for systems described above. That other structural factors may compete, or override, conformation



Scheme 7. Previously reported DPR of **21**.



Scheme 8. Correlation between selectivity and stability.



Scheme 9. Steroidal DPR.

issues is illustrated by the selectivity of steroidal dienone phenol rearrangements such as that of the steroidal dienone **27** depicted in Scheme 9 where **29** is the exclusive *p*-cresol product.[7] In the steroidal dienone–phenol rearrangement migratory aptitude plays the dominant role in determining product regiochemistry, overriding steric factors, which would appear to be more favorable in the disfavored pathway leading to the unobserved product **30**.

In conclusion, we have explored the dienone–phenol rearrangement of substrates where: only the *p*-cresol pathway was possible and relative migratory aptitudes should play no role in determining the regiochemistry of the reaction. For these substrates the selectivity of the rearrangement was found to correlate with the stereochemistry of the spirocyclic intermediate formed during the course of the rearrangement. Rearrangements employing substrates **11** and **12**, proceeding via spirocycle **16**, gave a 1:1 mixture of the two possible *p*-cresol products. In contrast, rearrangement of **10**, proceeding via the diastereomeric spirocycle **13**, gave—surprisingly—a single product **14**. It is tempting to attribute the selectivity of these rearrangements to the relative stability of cationic intermediates **17**–**20**, which lie on the pathway between spirocycle and final product. However, this correlation is obviously not perfect (otherwise substrates **11** and **12** would show some selectivity for product **15**) and more subtle issues may be at play here. Nevertheless, it seems that stereochemistry may play a more important role in determining the course of dienone–phenol rearrangement than previously recognized.

Acknowledgments

Support of this work by funds provided by the National Institutes of Health (R01 GM53172), the USDA/ARS-New Orleans (58-6425-8-084), and Louisiana State University is gratefully acknowledged. We thank Dr. Dale Treleaven, Dr. Frank Zhou and Mr. Guangyu Li for assistance with 2D NMR experiments and Dr. Frank Fronczek for assistance with X-ray crystallography.

Supplementary data

Experimental and ^{1}H NMR data for all compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.001.

References and notes

1. (a) Miller, B. Rearrangements of Cyclohexadienones. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience Publishers: New York, 1968; Vol. 1, pp 247–285; (b) Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245–256; (c) Woodward, R. B.; Singh, T. *J. Am. Chem. Soc.* **1950**, *72*, 494–500; (d) Woodward, R. B. In *Perspectives in Organic Chemistry*; Todd, A. R., Ed.; Interscience: New York, 1956; p 178; (e) Bloom, S. M. *J. Am. Chem. Soc.* **1958**, *80*, 6280; (f) Futaki, R. *Tetrahedron Lett.* **1964**, *41*, 3059–3064.
2. Shine, H. J.; Schoening, C. E. *J. Org. Chem.* **1972**, *37*, 2899–2901.
3. Sauer, A. M.; Fronczek, F. R.; Zhu, B. C. R.; Crowe, W. E.; Henderson, G.; Laine, R. A. *Acta Crystallogr., Sect. C* **2003**, *59*, o254–o256.
4. (a) Van der Gen, A.; Van der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav.Chim. Pays-Bas* **1971**, *90*, 1034–1044; (b) McMurry, J. E.; Musser, J. H.; Ahmad, M. S.; Blaszczak, L. C. *J. Org. Chem.* **1975**, *40*, 1829–1832.
5. (a) Revial, G.; Pfau, M. *Org. Synth.* **1992**, *70*, 35–46; (b) Tenius, B. S. M.; Oliveira, E. R.; Ferraz, H. M. C. *Tetrahedron: Asymmetry* **1993**, *4*, 633–636.
6. Hirakura, M.; Yanagita, M.; Inayama, S. *J. Org. Chem.* **1961**, 3061–3069.
7. Hanson, J. R.; Raines, D.; Knights, S. G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1311.