ORGANIC LETTERS

2003
Vol. 5, No. 20
3717−3719

Total Synthesis of 10-Norparvulenone and of *O*-Methylasparvenone Using a Xanthate-Mediated Free Radical Addition–Cyclization Sequence

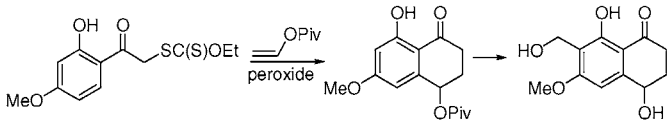
Alejandro Cordero Vargas, Béatrice Quiclet-Sire, and Samir Z. Zard*

Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91128 Palaiseau, France

zard@poly.polytechnique.fr

Received July 25, 2003

ABSTRACT



10-Norparvulenone

A short synthesis of (±)-10-norparvulenone and (±)-*O*-methylasparvenone was developed starting from commercially available *m*-methoxyphenol, hinging on a xanthate-mediated addition–cyclization sequence for the construction of the α-tetralone subunit.

The α-tetralone derivatives 10-norparvulenone (**1**)[1] and *O*-methylasparvenone (**2**)[2] are two natural products recently discovered, whose structures are characterized by a bicyclic carbon framework possessing a carbonyl function, one methoxy group, and two or three hydroxyl groups. (Figure 1).

10-Norparvulenone **1** is a novel anti-influenza virus antibiotic recently isolated from *Microsphaeropsis* sp., and preliminary in vitro assays have shown this compound to be a very promising anti-influenza virus drug.[1] To the best of our knowledge, there is as yet no total synthesis for this structure.

O-Methylasparvenone (**2**) exhibits very different pharmacological activities. It acts as a nitrogen-free serotonin antagonist and could be used in the treatment of depression and obsessive-compulsive disorders.[3] The synthesis of this natural product and some other analogues was reported by Bös et al.[3,4] In an interesting sequence, they were able to prepare compound **2** in seven steps from 3,4,5-trimethoxybenzaldehyde as starting material. Although this synthesis

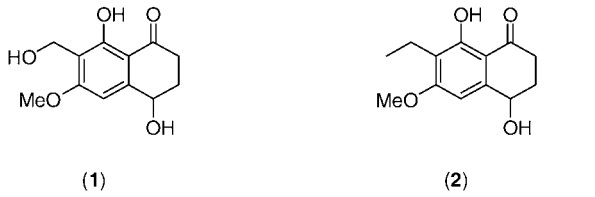


Figure 1.

is an effective way to prepare compound **2** and some analogues, it lacks flexibility and cannot, for example, be easily transposed to a synthesis of norparvulenone. In particular, the construction of the 4-hydroxy-1-tetralone motif was not straightforward. A few years ago, we reported a new method for the preparation of α-tetralones using xanthate free radical chemistry.[5] This method allows the synthesis of a wide variety of substituted tetralones under mild and neutral conditions. Herein, we report the first total synthesis of **1** and a new total synthesis of **2** using a xanthate-mediated free radical addition−cyclization sequence as the key step.

(1) Fukami, A.; Nakamura, T.; Kim, Y-P.; Shiomi, K.; Hyashi, M.; Nagai, T.; Yamada. H; Komiyama, K.; Omura, S. *J. Antibiot.* **2000**, *53*, 1215.

(2) (a) Simpson, T. J.; Stenzel, D. J. *J. Chem. Soc., Chem. Commun.* **1981**, 139. (b) Shan, R.; Stadler, M.; Anke, H.; Sterner, O. *J. Nat. Prod.* **1997**, *60*, 804.

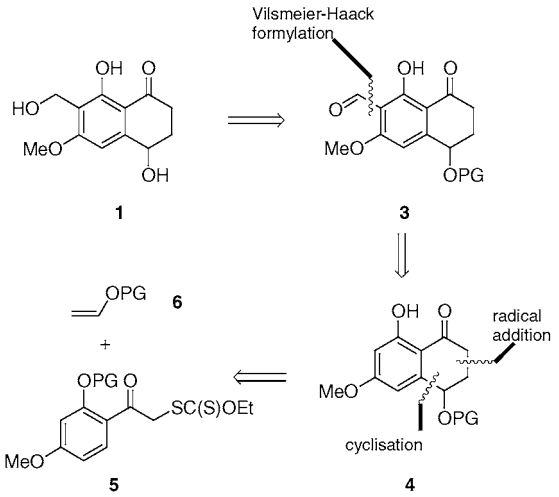
(3) Bös, M.; Canesso, R.; Inoue-Ohga, N.; Nakano, A.; Takehana, Y.; Sleight, A. J. *Bioorg. Med. Chem.* **1997**, *5*, 2165.

(4) Bös, M.; Stadler, H.; Wichmann, J.; Jenck, F.; Martin, J. R.; Moreau, J-L.; Sleight, A. J. *Helv. Chim. Acta* **1998**, *81*, 525.

10.1021/ol035394o CCC: $25.00
Published on Web 08/30/2003

Since no total synthesis has been reported for **1**, we first focused our attention on this compound. The general features of our route are outlined in Scheme 1. 10-Norparvulenone

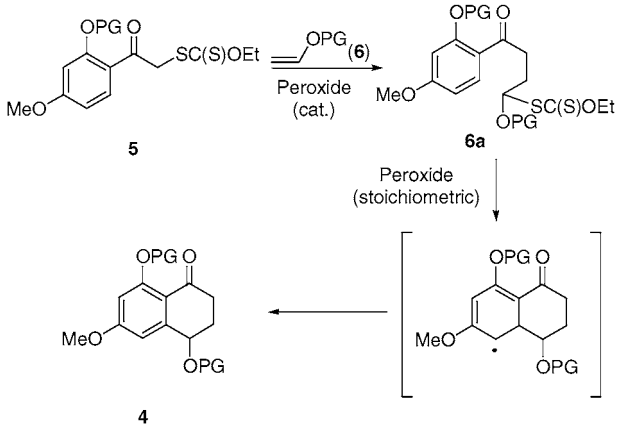
Scheme 1. Retrosynthetic Plan for Synthesis of **1**



(**1**) would be prepared from aldehyde **3** by simple reduction of the aldehyde and deprotection of the benzylic hydroxy group. To avoid selectivity problems in the formylation reaction, we planned to introduce the aldehyde function at a late stage in the synthesis.

A Vilsmeier−Haack formylation would allow us to obtain the desired aldehyde from **4**, which in the key step of the synthesis would be obtained in a convergent manner from an acetophenone xanthate (**5**) and the appropriate protected vinyl alcohol (**6**), the latter serving as an effective radical trap. The radical sequence for the synthesis of the key α-tetralone (**4**) is outlined in Scheme 2. We had shown that xanthates such as **5** could undergo a radical chain reaction to olefinic trap **6** to give adduct **6a** where a new carbon−carbon bond and carbon−sulfur bond have been formed.[6] This process has the great advantage that compound **6a** is

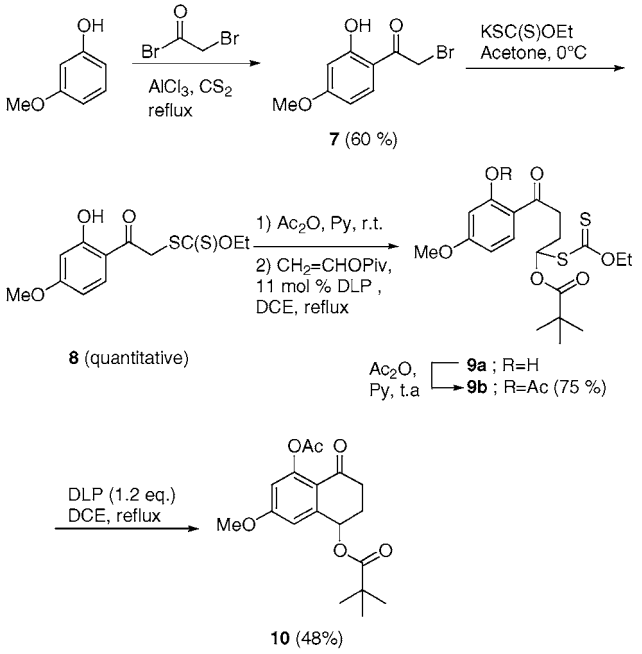
Scheme 2. Mechanism for the Radical Sequence



also a xanthate that can be used as a starting point for another radical sequence, in this case to construct the six-membered ketonic ring of α-tetralone **4**.

Our synthesis starts with the preparation of bromoacetophenone **7** in 60% yield by a Friedel−Crafts acylation of commercially available *m*-methoxyphenol using the conditions reported by Sawada et al.[7] (Scheme 3). Treatment of

Scheme 3. Preparation of Tetralone **9**



the latter with potassium ethyl xanthate in acetone at 0 °C afforded the desired radical precursor **8** in quantitative yield. The next step for the preparation of the key bicyclic intermediate **4** started with acetylation of the hydroxyl group followed by radical addition of the xanthate onto vinyl pivalate using dilauroyl peroxide (DLP) as initiator in 1,2-dichloroethane (DCE) as solvent, yielding a 1:1 mixture of the deprotected xanthate **9a** and the desired adduct **9b**. The former was converted into the latter under the same acetylation conditions. The overall yield of **9b** was 75% from **8**. When a refluxing solution of **9b** in DCE was treated with 1.2 equiv of DLP (added portionwise), tetralone **10** was obtained in 48% yield.

As can be seen in Scheme 3, partial deprotection of the phenolic group forced us to introduce an extra step in the reaction sequence. This problem was solved by simply adding acetic anhydride to the medium in the radical reaction, thus further demonstrating the tolerance and flexibility of xanthate chemistry.[6] This modification thus was incorporated

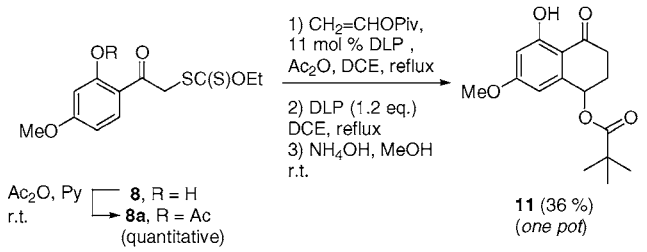
(5) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

(6) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1977**, *36*, 672. (b) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley VCH: Weinheim, 2001; p 90.

(7) Swada, S.; Miyasaka, T.; Arakawa, K. *Chem. Pharm. Bull.* **1977**, *25*, 3370.

in a one-pot conversion of xanthate **8a** into aldehyde precursor **4**. We therefore subjected **8a** to the three-step one-pot reaction sequence shown in Scheme 4 and obtained

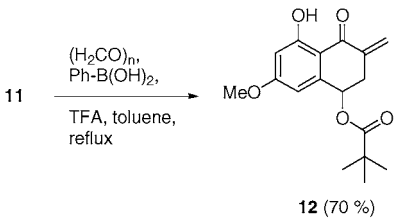
Scheme 4. One-Pot Preparation of Tetralone **11**



tetralone **11** in an overall yield of 36 % from **8** without optimization of the reaction conditions (Scheme 4).

The next step in our synthesis was the introduction of the formyl group in order to get the desired precursor of 10-norparvulenone (**1**). The application of one of the most common formylation reaction procedures, the Vilsmeier−Haack reaction[8] ($POCl_3$/DMF) to tetralone **11**, as well as some variations (PCl_5/DMF and $(COCl)_2$/DMF), were unsuccessful. We then attempted direct hydroxyalkylation of the phenol moiety. Application of the method reported by Nagata et al.[9] using paraformaldehyde and phenylboronic acid in refluxing toluene in the presence of trifluoroacetic acid (TFA) did not give the expected benzodioxaboronate but unsaturated ketone **12** instead (Scheme 5), probably via an aldol/dehydration

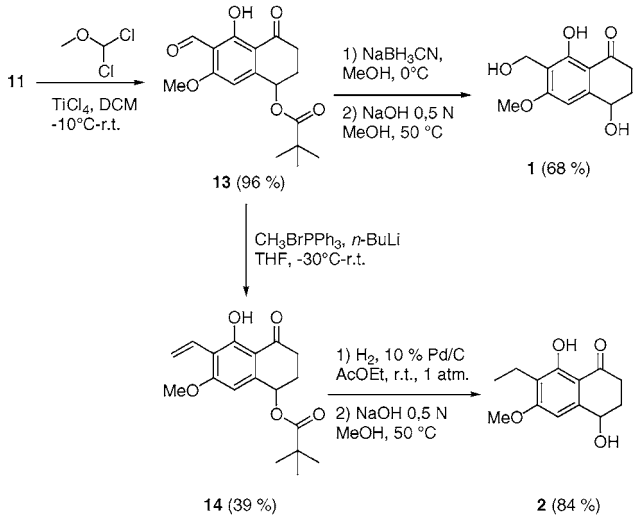
Scheme 5. Unexpected Formation of Compound **12**



reaction.[10] Even if this compound was not expected, it could be useful as a Michael acceptor for the synthesis of numerous analogues.

The introduction of the formyl substituent was finally achieved using the method described by Gross et al.[11] (Scheme 6). When a cold (−10 °C) solution of tetralone **11** in dichloromethane was treated with $TiCl_4$ and dichloromethyl methyl ether, aldehyde **13** was obtained in 96% yield. With precursor **13** in hand, completion of the synthesis of **1**

Scheme 6. Synthesis of (±)-10-Norparvlenone **1** and (±)-*O*-Methylasparvenone **2**



and **2** became straightforward. Thus, selective reduction of the aldehyde with $NaBH_3CN$ in methanol, followed by saponification of the trimethylacetyl ester group, furnished 10-norparvulenone **1** in 68% yield. The spectroscopic and analytical data of **1** were identical to those of the natural product.[1]

Because of the close relationship between **1** and **2**, we decided to use aldehyde **13** as the common intermediate for the synthesis of both natural products. Access to compound **2** was accomplished by converting the aldehyde into olefin **14** using typical Wittig conditions, without protection of the phenolic hydroxyl group. The yield was only moderate (39%), but having such a styrenyl group provides yet another handle for further manipulations. Hydrogenation over palladium on charcoal and saponification of the pivaloate group finally completed the sequence. In this way, (±)-*O*-methylasparvenone was isolated in 84% yield; its spectroscopic and analytical properties of **2** were identical to those reported in the literature.[3]

In conclusion, the first total synthesis of (±)-10-norparvulenone (**1**) has been accomplished in only five separate steps starting from commercially available *m*-methoxyphenol, with the final product isolated in 14% unoptimized overall yield. The total synthesis of (±)-*O*-methylasparvenone (**2**) required six steps from the same starting material with an overall yield of 7%. The strategy we have implemented is convergent, efficient, and highly flexible, allowing a great variety of modifications at several positions around the molecules.

Acknowledgment. We thank CONACyT for its generous financial support to A.C.V.

Supporting Information Available: Detailed description of experimental procedures and spectral information and analyses for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035394O

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