Tetrahedron Letters 49 (2008) 5268–5270

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tandem Diels–Alder-manganese dioxide mediated oxidation reaction. A short route to marcanines

Sabrina Mekideche, Laurent Désaubry *

UMR 7175-LC1, Université Louis Pasteur, CNRS, Department of Medicinal Chemistry, Faculté de Pharmacie, 74 Route du Rhin, BP 60024, 67401 Illkirch, France

ARTICLE INFO

Article history:
Received 15 May 2008
Revised 19 June 2008
Accepted 24 June 2008
Available online 28 June 2008

Keywords:
Azaanthraquinones
Tandem reactions
Diels–Alder
Anticancer natural products

ABSTRACT

An efficient synthesis of anthraquinones by a tandem Diels–Alder-decarboxylation-manganese dioxide mediated oxidation reaction was developed and applied to the regioselective synthesis of an azaanthraquinone.

Topoisomerase II inhibitors are highly efficacious antineoplastic agents for various hematopoietic and solid tumors.[1] However, their usefulness is limited by their cardiotoxicity, and the search of new topoisomerase II inhibitors with lower side effects remains an active field of research.[2] In a previous article, we presented electrochemical data that suggest that dielsiquinone (Fig. 1, **1**), a potent cytotoxic natural product related to anthracyclines, should be less cardiotoxic than anthracyclines used in clinic, and may therefore provide the basis for the development of safer anticancer drugs.[3] In 1999, Suwanborirux reported the isolation of secondary metabolites related to dielsiquinone from the stem bark of *Goniothalamus marcanii*, a rare small tree growing in Thailand.[4] Among these, marcanine D displayed cytotoxic activities superior to that of dielsiquinone against a variety of tumor cells. Unfortunately, this compound could not be isolated in sufficient amount to record a complete ^{13}C NMR spectrum and to characterize it unambiguously. A NOE effect between the hydroxyl proton and the 4-methyl protons suggested that this compound should be **2**, but on handling trace amounts of material some errors may occur.

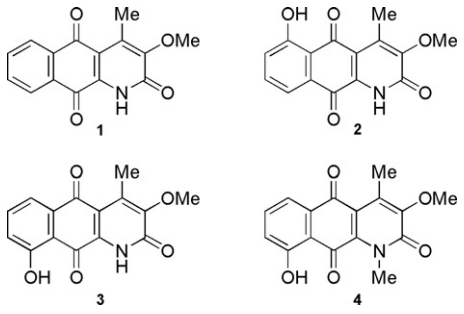


Figure 1. Dielsiquinone (**1**), proposed (**2**), and alternative (**3**) structures of marcanine D and marcanine E (**4**).

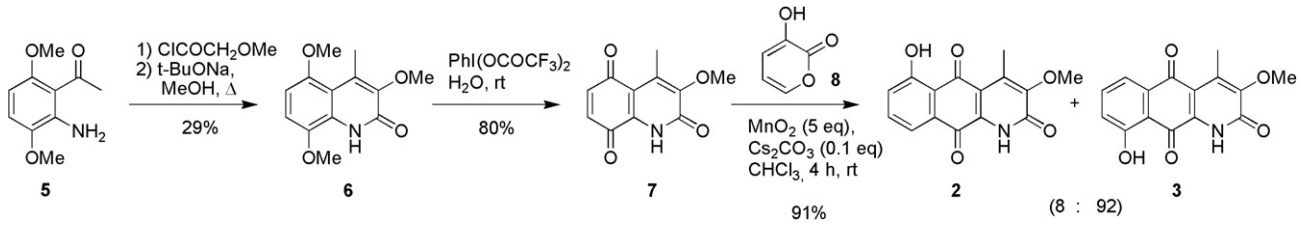
The identification of marcanine E (**4**) in the same extract from the stem bark suggested that the structure of marcanine D might also be **3**. The uncertainty of its structure, coupled with its natural scarcity and therapeutic potential, prompted us to undertake the synthesis of **2** and **3**.

Attempts to synthesize **2** according to the strategy that we developed for **1** were unsuccessful.[3] We now had to identify a new way to create the heterocyclic core of these compounds. Our new approach was based on the synthesis of naphthoquinones by the base–catalyzed Diels–Alder reaction hydroxypyrone **8** with quinones, which was recently developed by Tsuboi and coworkers.[5]

The synthesis of quinone **7** started with acylation of known amine **5** (two steps from commercial 2,5-dimethoxyacetophenone),[6] followed by cyclization under basic conditions to yield quinolone **6** (29% for two steps) (Scheme 1). Attempts to oxidize **6** to the quinone **7** with ceric ammonium nitrate under classical conditions[7] gave unsatisfactory yields (⩽24%), due to an extensive degradation of the compound. Use of silver(II) dipicolinate developed for acid-labile products slightly increased the yield to 34%.[8] Gratifyingly, oxidative demethylation of **6** with phenyliodine(III) bis(trifluoroacetate)[9] in water afforded the quinone **7** in an 80% yield.[10]

* Corresponding author. Tel.: +33 390 244 141; fax: +33 390 244 310.
E-mail address: desaubry@chimie.u-strasbg.fr (L. Désaubry).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.107



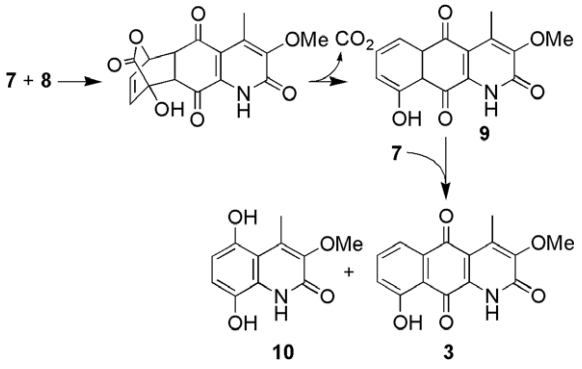
Scheme 1. Synthesis of Marcanine D.

Initial attempts to perform the tandem Diels–Alder-decarboxylation reaction of 3-hydroxypyrone **8** with quinone **7** afforded a mixture of the adducts **2** and **3** with a regioselectivity of 8:92 albeit with yields inferior to 45%.[11] Similar good regioselectivities have been observed in the Diels–Alder reaction of related azaanthraquinones with other types of diene.[12]

The presence of dihydroquinone **10** in the reaction medium indicated that these low yields stem from the oxidation of the intermediate **9** by the starting quinone **7** (Scheme 2). In their synthesis of naphthoquinones, Tsuboi and co-workers performed the Diels–Alder reaction of hydroxypyrone **8** with unexpensive quinones, which were used in excess to oxidize the adduct to the corresponding naphthoquinone.[5]

Attempts to oxidize in situ **9** by DDQ were not satisfactory. Inspired by the use of manganese dioxide in tandem oxidation/olefination recently developed by Taylor et al.,[13] we added over 4 h a solution of quinone **7** to a mixture of hydroxypyrone **8**, Cs_2CO_3, and MnO_2, with the hope that the intermediate **9** would be oxidized in situ by MnO_2. As far as we know, such an in situ MnO_2 oxidation of a Diels–Alder adduct had never been described previously. To our greater delight, this reaction proceeded with a 91% yield affording **2** and **3** in an 8:92 ratio.[14]

The structure of **3** was confirmed by NOE between H-5 (δ 7.57 ppm) and Me-4 (δ 2.51 ppm) and by key HMBC correlations from these protons and the C-10 carbonyl carbon at δ 182 ppm (Fig. 2).



Scheme 2. Proposed mechanism to explain the low yield of the Diels–Alder reaction in absence of MnO_2.

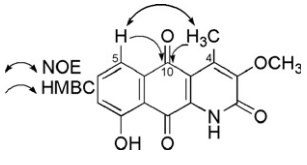


Figure 2. Key NOE and HMBC correlations of **3**.

Compounds **2** and **3** were compared by HPLC–MS with an authentic sample of marcanine D generously provided by Pr. Suwanborirux. Unfortunately, this sample had been too degradated over time to prove unambigously the structure of marcanine D. However, **2**, but not **3**, displayed the same retention time and the same mass spectrum as one of the compounds present in this sample, which tends to confirm that the structure of marcanine D is really **2**.[15]

In conclusion, we described herein a concise synthesis of marcanines based on a new construction of anthraquinones by a tandem Diels–Alder-decarboxylation-manganese dioxide mediated oxidation reaction of quinone **7** with hydroxypyrone **8**.

Acknowledgments

We would like to dedicate this Letter to Professor Miguel Yus for his 65th birthday. We are extremely grateful to Pr. Khanit Suwanborirux for providing an authentic sample of marcanine D. We thank Cyril Antheaume, Roland Graff and Patrick Wehrung for NMR spectroscopic and mass spectrometric assistance.

References and notes

1. Minotti, G.; Menna, P.; Salvatorelli, E.; Cairo, G.; Gianni, I. *Pharmacol. Rev.* **2004**, *56*, 185–229.
2. Denny, W. A. *Expert. Opin. Emerg. Drug.* **2004**, *9*, 105–133.
3. Brisach-Wittmeyer, A.; Sani Souna Sido, A.; Guilini, P.; Désaubry, L.*Bioorg. Med. Chem. Lett.* **2005**, *15*, 3609–3610.
4. Soonthornchareonnon, N.; Suwanborirux, K.; Bavovada, R.; Patarapanich, C.; Cassady, J. M. *J. Nat. Prod.* **1999**, *62*, 1390–1394.
5. Komiyama, T.; Takaguchi, Y.; Tsuboi, S. *Synlett* **2006**, 124–126.
6. Bandurco, V. T.; Schwender, C. F.; Bell, S. C.; Combs, D. W.; Kanojia, R. M.; Levine, S. D.; Mulvey, D. M.; Appollina, M. A.; Reed, M. S.; Malloy, E. A.; Falotico, R.; Moore, J. B.; Tobia, A. J. *J. Med. Chem.* **1987**, *30*, 1421–1426.
7. Castagnoli, N., Jr.; Shulgin, A. T.; Callery, P. S.; Jacob, P., III *J. Org. Chem.* **1976**, *41*, 3627–3629.
8. Syper, L.; Mlochowski, J.; Kloc, K. *Tetrahedron* **1983**, *39*, 781–786.
9. Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899–6902.
10. *Experimental procedure for the synthesis of quinone* **7**: A suspension of dimethoxyarene **6** (99 mg, 0.4 mmol) and phenyliodine(III) bis(trifluoroacetate) (3.4 g, 0.8 mmol) in 2 ml of water and 50 μl MeOH was sonicated at rt for 1.5 h (the water of the bath was changed every 15 min to keep the medium at rt). The medium was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/acetone 9:1) to give 70 mg (3.2 mmol, 80%) of quinone **7** as red crystals. ^{1}H NMR (300 MHz, DMSO-d_6): 6.92 (d, J = 10.0 Hz, 1H), 6.83 (d, J = 10.0 Hz, 1H), 3.83 (s, 3H), 2.40 (1s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 185.0, 179.6, 156.9, 150.7, 139.3, 135.6, 135.2, 133.8, 113.5, 59.0, 13.0. IR (KBr): 2921, 2854, 1511, 1519, 1364, 1223, 1035, 986, 933, 849 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.22; H, 4.21; N, 6.33.
11. Initial attempts to perform the Diels–Alder reaction of **8** with **7** were performed in presence of Cs_2CO_3 in $CHCl_3$ at rt for 3 h.
12. (a) Pérez, J. M.; Vidal, L.; Grande, M. T.; Menéndez, J. C.; Avendaño, C. *Tetrahedron* **1994**, *50*, 7923–7932; (b) del Mar, M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1997**, *53*, 11465–11480.
13. Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851–869.
14. *Experimental procedure for the synthesis of* **2** *and* **3**: To a mixture of 3-hydroxy-2-pyrone **8** (112 mg, 1 mmol), manganese dioxide (433 mg, 5 mmol), and Cs_2CO_3 (19 mg, 0.1 mmol) in $CHCl_3$ (4 ml) was added a solution of quinone **7** (110 mg, 0.5 mmol) in $CHCl_3$ (5 ml) at r.t. over a period of 4 h by using a syringe

pump. The mixture was stirred at rt for an additional 20 min, filtered on Celite (washing with $CHCl_3$), and concentrated. The residue was purified by silica gel chromatography (CH_2Cl_2/EtOAc/toluene 8:1:1) to afford 130 mg (91%) of a mixture of adducts **2** and **3** in an 8:92 ratio as an orange solid. For spectroscopic analyses of **2** and **3**, pure samples were purified by RP-HPLC.
Compound **2**: ^{1}H NMR (400 MHz, DMSO-d_6): 7.77 (dd, J = 8.0 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 3.88 (s, 3H), 2.49 (s, 3H); UV (DMSO) λ_{max} 277, 306 nm; MS (ESI): m/z 286.1 $(M+H)^+$, 308.1 $(M+Na)^+$, 593.0 $(2M+Na)^+$.
Compound **3**: ^{1}H NMR (300 MHz, DMSO-d_6): 7.93 (s, 1H), 7.74 (dd, J = 8.4, 7.5 Hz, 1H), 7.57 (dd, J = 7.5, 1.0 Hz, 1H), 7.29 (dd, J = 8.4, 1.0 Hz, 1H), 3.87 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 181.5, 181, 160, 157, 151, 136, 135, 137, 133, 123, 119, 117, 114, 59, 13; UV (CH_3CN) λ_{max} 274, 302 nm; MS (ESI): m/z 286.1 $(M+H)^+$, 308.1 $(M+Na)^+$, 593.0 $(2M+Na)^+$.

15. The difficulty to obtain a sample of the stem bark of *Goniothalamus marcanii*, which is a rare tree growing in Thailand, prevented us to compare **2** and **3** with a freshly extracted sample of marcanine D.