Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 837–844

# Synthetic approach to pentacyclic quassinoids from communic acids, via ambracetal derivatives

E. J. Alvarez-Manzaneda,[a,*] J. L. Romera,[a] A. F. Barrero,[a] R. Alvarez-Manzaneda,[b] R. Chahboun,[a] R. Meneses[a] and M. Aparicio[b]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain*
[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Almería, 04120 Almería, Spain*

Received 26 June 2004; revised 12 November 2004; accepted 15 November 2004

Available online 30 November 2004

**Abstract**—Methyl (8*R*,13*S*)-8α,13:13,17-diepoxy-14,15-dinorlabdane-19-oate, easily prepared from communic acids, is a suitable intermediate for synthesizing pentacyclic quassinoids, because it enables the elaboration of the A ring and the further construction of the B–C–D ring system of these terpenoids. The cetal group is stable under the reaction conditions utilized during the elimination of the ester group and the introduction of the hydroxyl group on C-3. At the same time, it enables the regeneration of the methylketone and exocyclic double bond presented by methyl 13-oxo-14,15-dinorlabd-8(17)en-19-oate. The latter compound was previously used to construct the B–C–D-ring of these quassinoids.


## 1. Introduction

In a previous paper we reported the efficient preparation of the tetracyclic derivative **3**, a possible intermediate in the synthesis of pentacyclic quassinoids from communic acids (**1a–c**) via methylketone **2** (Scheme 1).[1] **3** presents the B, C and D rings suitably functionalized to construct the B–C–D–E framework of such quassinoids, but the elaboration of the A ring of quassinoids from this intermediate is likely to be difficult. Thus we have investigated how to functionalize the A ring during the early steps of the synthetic sequence, before creating the B–C–D–E system. We believed that cetal **4**, the preparation of which, from **1a–c** in a 3-step sequence, we have reported elsewhere, [1,2] could well be suitable for this purpose. Cetal **4**, bearing the methylketone and exocyclic double-bond groups as masked functions, would allow us to functionalize the A ring according to the method we have described previously.[3] Thus, the functionalized cetal **A** would be prepared and then the regeneration of methylketone and the exocyclic double bond would lead to **B**, which, following the previously developed synthetic sequence utilized to convert **2** into **3**,[1] would provide the tetracyclic intermediate **C**. The whole ring of this compound is suitably functionalized, and thus pentacyclic quassinoids, as bruceantin, may be obtained (Scheme 1).

In this paper we report a procedure to create the methylketone and exocyclic double bond groups from the cetal function in **4**, in addition to two methods to functionalize the A ring of **4**.

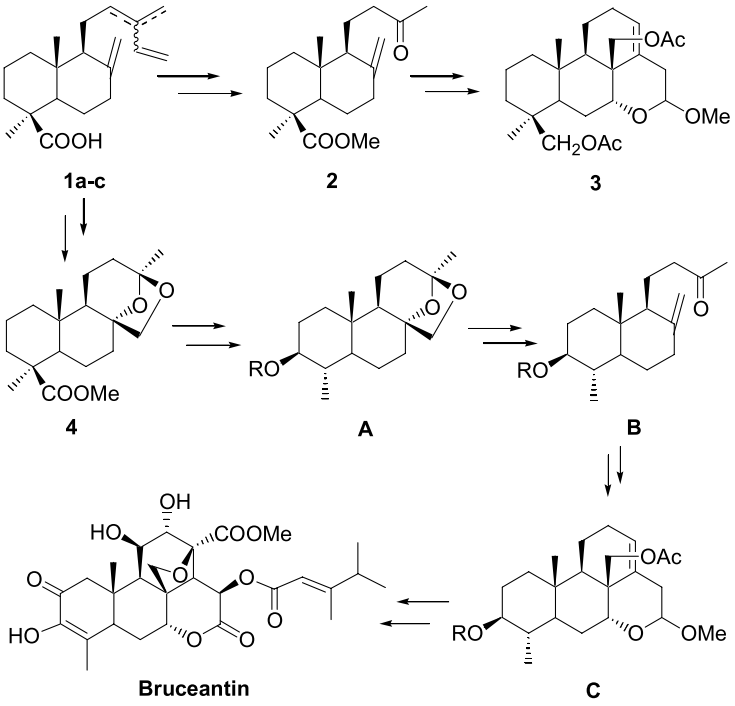
## 2. Results and discussion

We began by investigating methods to create methylketone and exocyclic double-bond groups from cetal **4**, the preparation of which from **1a–c** via the reduction derivatives **5a–b**, has now been considerably improved. **5a–b** was converted into **4** in one-pot reaction, without isolating the intermediate methylketone **2**. Our previous studies revealed that the $TiCl_4$-catalysed nucleophilic cleavage of cetal could be used to this end.[4] We assayed the reaction of **4** with $TiCl_4$ in the presence of $Et_3SiH$ as the nucleophile under various conditions.[5] The most significant results are shown in Table 1 (Scheme 2). As can be seen, good yields of oxane derivatives **6a–b** were always obtained. Formate **7** showed similar reactivity, affording a 1:1 mixture of oxanes **8a–b** when treated at −78 °C.

The epimeric mixture **6a–b** was used as the starting material to prepare methylketone **2**. The key step in the sequence was the C–O cleavage of the α-alkoxyaldehydes **9a–b** under

*Keywords*: Quassinoids; Labdane diterpenes; Acetal cleavage; Wolff–Kishner elimination.
* Corresponding author. Tel./fax: +34 958 24 80 89; e-mail: eamr@ugr.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.11.034




**Scheme 1.**

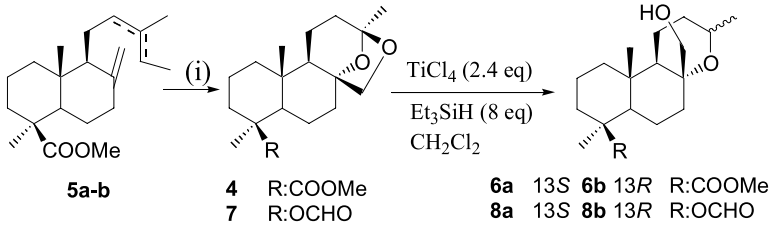
**Table 1**. Treatment of **4** with $TiCl_4$–$Et_3SiH$ in $CH_2Cl_2$

| Entry | Reaction time (h) | Temperature | **6a–6b** (% conversion) |
|---|---|---|---|
| 1 | 1 | −78 °C | 1:1 (95%) |
| 2 | 2 | rt | 1:6 (96%) |
| 3 | 14 | rt | 0:1 (70%) |

Wolff–Kishner reduction conditions (Scheme 3).[6] The treatment of **6a–b** with PCC in $CH_2Cl_2$ at room temperature afforded aldehydes **9a–b**, which, by treating with KOH and $H_2NNH_2$ in triethylene glycol at 160 °C for 2 h, yielded a mixture of alcohols **10a–b**, after esterification with diazomethane. These were transformed into methylketone **2** by Jones' reagent. In a similar way **8a–b** was transformed into methylketone **13**.

After the procedure to transform cetals **4** and **7** into the corresponding methylketones **2** and **13** had been established, we undertook the functionalization of the A rings of **4** and **7**. Two synthetic sequences were developed to achieve our objective, the key step of both being the Baeyer–Villiger rearrangement of aldehyde **15** to give the formate **7**.[3] The refluxing of a solution of **15** in $CH_2Cl_2$ in the presence of MCPBA afforded formate **7**, which underwent the regioselective elimination of formic acid by heating with collidine, thus yielding **16**. The treatment of **16** with $SeO_2$–*t*BuOOH in $CH_2Cl_2$ gave alcohol **17** which was converted into ketone **18** after oxidation with PCC, reduction with Raney nickel[7] and epimerization with MeONa in MeOH (Scheme 4).

We also assayed an alternative route to **18** from **7**, involving saponification, dehydration and oxidation. By treating **7** with KOH in methanol we obtained *nor*-alcohol **19**. The dehydration of **19** with MsCl and pyridine at room temperature yielded a 1:4 mixture of regiosomers **16** and **20**. By treating this under reflux with $Na_2CrO_4$ in the presence of NaAcO, $Ac_2O$ and AcOH we obtained β-enone **21**, the exocyclic alkene **16** being recovered unaltered. The β-enone **21** was transformed under Birch reduction conditions into ketone **18**, which, after reduction with sodium borohydride, was transformed into **22**, which bears the characteristic A-ring functionalization pattern of the postulated intermediates in the synthesis of pentacyclic quassinoids,[8] with the appropriate configuration on C-3 and C-4 (Scheme 5).




**Scheme 2.** Reagents and conditions: (i) $OsO_4$ 0.2%, *t*BuOH–$H_2O$, rt, 15 min; NaIO4, 90 °C, 16 h; Jones, acetone, rt, 3 h (80%).