Tetrahedron Letters 50 (2009) 3359–3362

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Studies related to the total synthesis of the sesquiterpene core of the pyrrolobenzoxazine natural products CJ-12662 and CJ-12663

Małgorzata Commandeur [a], Claude Commandeur [a], Michael De Paolis [a], Andrew J. F. Edmunds [b], Peter Maienfisch [b], Léon Ghosez [a,*]

[a] *Institut Européen de Chimie et Biologie, UMR 5248-CNRS, 2, rue Robert Escarpit, 33607 Pessac, France*
[b] *Syngenta Crop Protection, Muenchwilen AG WST-820.1.15, Schaffhauserstrasse, CH-4332 Stein, Switzerland*

ARTICLE INFO

Article history:
Received 10 February 2009
Accepted 13 February 2009
Available online 21 February 2009

Keywords:
[2+2] Cycloaddition
Ring-opening metathesis/cross metathesis
Phenyl-1-propynyl sulfide
Cyclohexenone
Stereoselectivity
$TMSNTf_2$
Terpenoid pyrrolobenzoxazine alkaloid
CJ-12662
CJ-12663

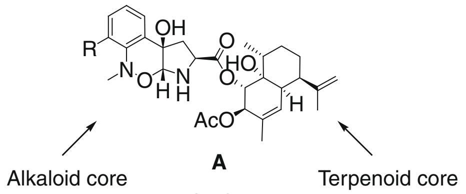
ABSTRACT

A highly effective procedure is reported to synthesize a substituted bicyclo[4.2.0]octenol derivative by regioselective cycloaddition of phenyl-1-propynyl sulfide with cyclohexenone followed by selective reduction of the ketone group and reductive elimination of phenylsulfonyl group. The strained cyclobutene ring was then engaged in a ring-opening/cross metathesis sequence in the presence of Hoveyda–Grubbs 2nd generation catalyst. The synthesis serves as a model study toward the synthesis of the sesquiterpene diol portion of the terpenoid pyrrolobenzoxazine alkaloids, CJ-12662 and CJ-12663.

Natural product alkaloids of the general formula **A** (Fig. 1) have been isolated from the fermentation broth of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618.[1] They belong to a unique class of terpenoid pyrrolobenzoxazine alkaloids which display broad anti-parasitic and antibiotic properties. A single-crystal structure determination established that CJ-12662 and CJ-12663 contain a pyrrolobenzoxazine carboxylic acid esterified with a sesquiterpene diol (Fig. 1).[2]

The alkaloid cores of CJ-12662 and CJ-12663 have been synthesized by the groups of Barrett and Baldwin, respectively.[2,3] There are currently no reports on the total synthesis of the sesquiterpene core of these natural products. This challenging terpenoid structure is a *cis*-decalin containing no less than six stereocenters and three contiguous oxygenated functional groups. The general strategy we have envisioned for the total synthesis of this terpene is depicted in Scheme 1. We had planned to construct ring A and the *cis*-diol by a stereodirected pinacol coupling (disconnection a).

The most challenging part of the synthesis is the stereoselective construction of the two vicinal olefinic side chains with simultaneous control of the configuration of the double bond of the allylic acetate. The cis-relationship between the two vicinal carbon chains could be established by a regio- and stereoselective cycloaddition reaction (step d) of an activated acetylene to the less hindered face of (*R*)- 6-methylcyclohexenone. A ring opening metathesis of the cyclobutene ring coupled with a cross metathesis (step c) with an allylic acetate derived (step e) from (*R*)-glyceraldehyde would generate an advanced intermediate for the pinacol coupling. This Letter reports some model studies on the cycloaddition and ROM/CM reactions performed on cyclohexenone.



A
R = Cl, **CJ-12662**
R = H, **CJ-12663**

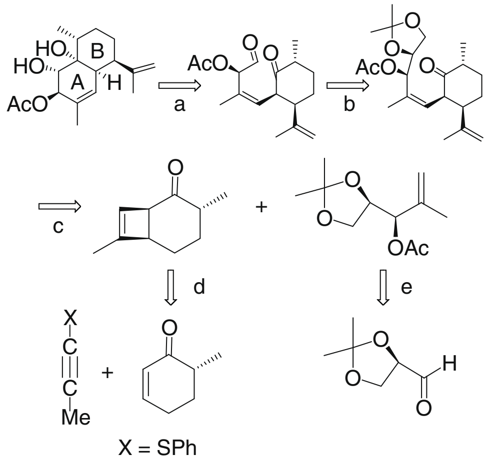
Figure 1. Structure of terpenoid pyrrolobenzoxazine alkaloids CJ-12662 and CJ-12663.

[2+2] Cycloadditions of acetylenes to electron-deficient olefins have been studied by several groups.[4] Best yields have been obtained in the presence of a Lewis acid catalyst. We selected

---

* Corresponding author. Tel.: +33 5 4000 2217/2223; fax: +33 5 4000 2215.
E-mail address: l.ghosez@iecb.u-bordeaux.fr (L. Ghosez).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.105



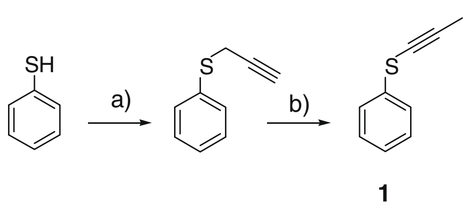
Scheme 1. Retrosynthetic analysis of the terpenoid core of CJ-12662 and CJ-12663.

phenyl-1-propynyl sulfide (X = PhS) as acetylene partner to ensure (a) the activation of the triple bond, (b) the control of the regioselectivity of the cycloaddition, (c) an easy replacement of the X substituent by hydrogen. Phenyl-1-propynyl sulfide **1** was prepared in two steps inspired by literature procedure (Scheme 2).[5]

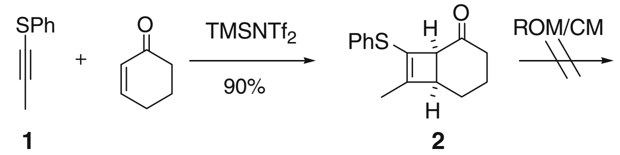
It was found that the cycloaddition of **1** with cyclohexenone took place readily in the presence of 10 mol % of $TMSNTf_2$ (Scheme 3). A single regio- and stereoisomer (**2**) was obtained in 90% yield after one hour at −40 °C.[6] Here again $TMSNTf_2$ was found superior[7] to TMSOTf and the corresponding Brönstedt acids HOTf and $HNTf_2$. These showed a much lower catalytic activity (reaction time > 1 day) and gave lower yields (45 to 65%).

We then explored the ring-opening metathesis/cross metathesis sequence by reacting adduct **2** with acrylonitrile, α-methyl acrylonitrile or 2-methylprop-2-enol in the presence of Grubbs and Hoveyda–Grubbs 2nd generation catalysts.[8,9] Compound **2** was recovered unaffected in each case (Scheme 3). Precedents for metathesis reaction with substrates carrying sulfide had however been reported.[10] Thus, the poor reactivity of **2** probably resulted from the high degree of substitution of the cyclobutene double bond. Therefore, the phenylsulfide group has to be removed before the ROM/CM reactions.

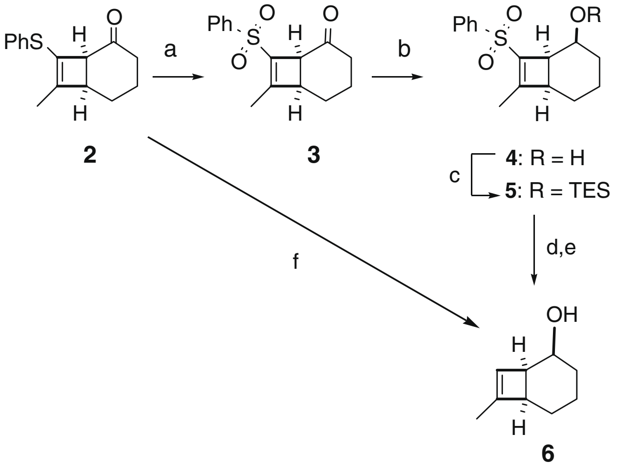
To this aim, oxidation of **2** with *m*-CPBA gave the corresponding phenylsulfone **3** in 72% yield (Scheme 4, step a). Treatment of **3** with activated magnesium turnings resulted in a slow reductive elimination of the phenylsulfone group with concomitant reduction of the ketone group to yield **6** (29%) as a mixture of epimeric alcohols.[11] A much better procedure consisted of a stereoselective reduction of the ketone group of crude **3** with sodium borohydride (step b) yielding a single alcohol **4** where the OH group is cis with respect to the cyclobutene ring (86% for two steps). The relative configuration of **4** has been confirmed by X-ray diffraction analysis (Fig. 2).[12]



Scheme 2. Reagents and conditions: (a) NaOH (1.7 equiv), propargyl bromide (1 equiv), TBAB (10 mol %), H_2O, 0 °C, 4 h; (b) *t*-BuOK (1.5 equiv), *t*-BuOH, 50 °C, 10 min (86%, 2 steps).



Scheme 3. Cycloaddition step.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 10 min; (b) $NaBH_4$, MeOH, −40 °C, 1 h; (c) TESCl, imidazole, CH_2Cl_2, 0 °C, rt, 12 h (87% for 3 steps); (d) activated Mg, MeOH, 50 °C, 1 h; (e) TBAF, THF, 2 h (91% for 2 steps); (f) *steps (a), (b) and (d) sequentially performed without purification of any intermediate*.

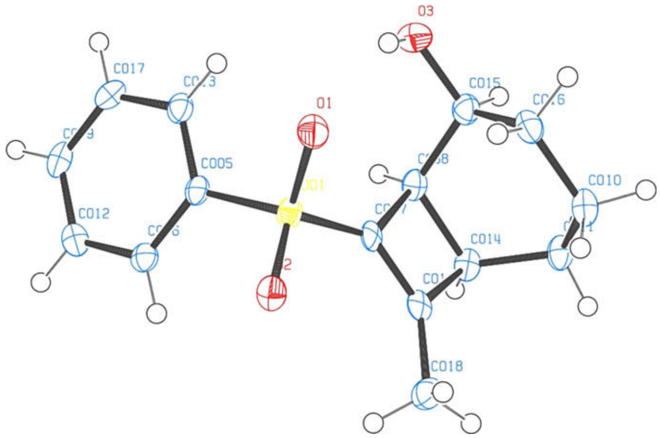


Figure 2. Ortep drawing of **4**.

Subsequent removal of the phenyl sulfone with activated magnesium turnings (step d) led to **6** but again only in poor yields. However, it was found that protection of the alcohol function (step c) followed by treatment of the resulting triethylsilyl ether **5** with activated magnesium turnings in methanol at 50 °C (step d) gave the target alcohol **6** after desilylation with tetrabutylammonium fluoride (step e). Optimization of this reaction sequence (Scheme 4, step f) led to a 70% yield for the synthesis of diastereomerically pure **6** from **2** *without purification of any intermediate.*

The ring opening metathesis of unsubstituted and monosubstituted double bonds of cyclobutenes followed by cross-metathesis with unsubstituted terminal olefins has been extensively studied by Snapper et al.[13] The factors effecting regioselectivity of the ring opening and the stereoselectivity of the formation of the new double bond have been studied in detail, and have shown to be depen-