DOI: 10.1002/ejoc.200700648

An Expeditious Assembly of 3,4-Benzannulated 8-Oxabicyclo[3.2.1]octane Systems by [2+2+2] Alkyne Cyclotrimerisation: Total Synthesis of (–)-Bruguierol A

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Dedicated to Professor Andrea T. Vasella on the occasion of his 65th birthday

Keywords: Total synthesis / Epoxidation / Cyclotrimerisation / Wilkinson's catalyst

Facile construction of benzene-fused 8-oxabicyclo[3.2.1]octane systems by employing a cross alkyne cyclotrimerisation reaction was explored. With this procedure, (–)-bruguierol A was synthesised, and its absolute configuration was established.

Introduction

Since its first disclosure by Reppe et. al,[1] the transition-metal-catalysed [2+2+2] alkyne cyclotrimerisation reaction[2] has become an integral component in the armoury of organic synthetic methods. The utility of this reaction is exemplified in the synthesis of a variety of complex natural products comprising aromatic rings,[3] dendritic ensembles,[4] and cyclophanes[5] with variable sizes. Recent progress in this context includes the development of water-soluble catalysts[6] and a variety of chiral ligands for the asymmetric version[7] of this transformation. Various transition metals (e.g. Ni, Rh, Co, Pd, Cr, Fe, Ru and Ta) as well as Ziegler-type catalysts have been recognised to promote inter- and intramolecular versions of the cyclotrimerisation reaction.

Vollhardt and coworkers showed the feasibility of the intramolecular [2+2+2] cycloaddition reaction of enediynes for the synthesis of highly strained [3.2.1]bicyclooctanes;[8] however, the scope of this reaction in the synthesis of bridged bicyclic systems has seen limited potential. Very recently, Malacria and coworkers explored the possibility of this intramolecular [2+2+2] cyclisation approach for the tandem construction of the B, C, D and E rings of the polycyclic taxane system.[9] To the best of our knowledge, no report on intermolecular [2+2+2] cyclisations leading to bridged bicycles has been documented. Herein we report the application of intermolecular [2+2+2] alkyne cyclotrimerisation reactions for the construction of benzannulated 8-oxabicyclo[3.2.1]octane systems. Our initial foray into this area was stimulated by the recently isolated natural products bruguierol A–C (**1**–**3**, Figure 1), which portrayed this new 3,4-benzannulated 8-oxabicyclo[3.2.1]octane structural skeleton.[10] The most general methods used to access the oxabicyclo[3.2.1]octane systems are [4+3] cycloadditions and annulations.[11,12] Marson and coworkers reported a general route to bridged bicyclo ethers by tandem cyclisations involving 3,4-epoxy alcohols.[13]

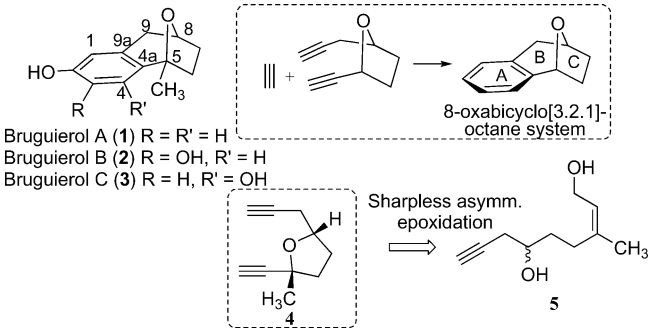

Figure 1. Structures of bruguierol A–C and the key [2+2+2] cyclotrimerisation reaction for the creation of the 8-oxabicyclo[3.2.1]octane system.

Bruguierol A–C were isolated and characterised by Sattler and coworkers from the stem of *Bruguieragymnorrhiza*, which was collected from the coast of Xiamen in the south of China.[10] Amongst the three, bruguierol C showed moderate activity against Gram-positive and Gram-negative bacteria including mycobacteria and resist-

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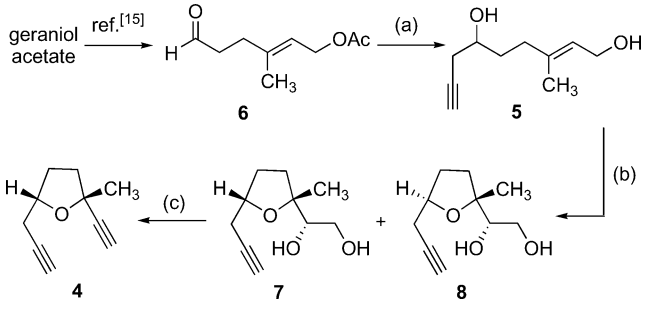
ant strains (MICs 12.5 $\mu g\,mL^{-1}$). Extensive structural investigation with various 2D NMR spectroscopic techniques was carried out on **1**–**3** to elucidate their constitution and relative stereochemistry; however, complete absolute stereochemical characterisation was hampered by the lack of a suitable functional group handle on the bicyclic framework that could be derivatised according to either the Mosher method or other related methods to establish the absolute configurations indirectly. This communication describes the first total synthesis of (–)-bruguierol A (**1**) with its absolute stereochemistry.

Strategically, with the consideration that the cyclotrimerisation reaction would build the A and B rings of the tricyclic core (Figure 1), diyne **4** was identified as the key intermediate. Because the absolute configuration of natural bruguierol was unknown, we decided to use the chiral structure of **4** as depicted in the Figure 1. Kinetic resolution of a 6-substituted hex-2-en-1,6-diol (**5**) by means of Sharpless asymmetric epoxidation was chosen for the synthesis of **4**.[14]

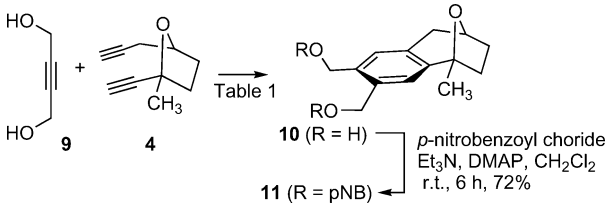
Results and Discussion

The synthesis started with the propargylation of known 6-acetyloxy-4-methylhex-4-enal (**6**)[15] under Barbier conditions (Scheme 1)[16] to afford **5**. The following Sharpless asymmetric epoxidation[14c] reaction proceeded well under standard conditions and gave easily separable isomeric furans **7** and **8** in 90% yield and with 91 and 90% *ee*, respectively (see Supporting Information for details). The $NaIO_4$-mediated cleavage of required *cis* furan diol **7** followed by treatment of the intermediate aldehyde with the Ohira–Bestmann reagent[17] gave key diyne **4** in 82% yield.



Scheme 1. Reagents and conditions: (a) 1. propargyl bromide, Zn, saturated aqueous NH_4Cl, THF, 0 °C → r.t., 2 h, 87%; 2. K_2CO_3, methanol/water, r.t., 4 h, 90%; (b) L-(+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, DCM, –20 °C, 6 h, 90%; (c) 1. silica-supported $NaIO_4$, DCM, r.t., 2 h; 2. dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, methanol, r.t., 4 h, 82%.

With the fully elaborated diyne framework of **4** in place, the task of cyclotrimerisation with another alkyne was attempted by using easily available 2-butyne-1,4-diol (**9**). After screening few catalysts, Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] was found to effect the cyclotrimerisation reaction of **4** with **9** (Scheme 2) effectively at 80 °C and afforded **10** in 85% yield.[18] This was derivatised as its *p*-nitrobenzoate to obtain crystalline dibenzoate **11**, and this compound was characterised by single-crystal X-ray structural analysis (Figure 2).[21]



Scheme 2. Cyclotrimerisation of diyne **4** and 2-butyne-1,4-diol (**9**).

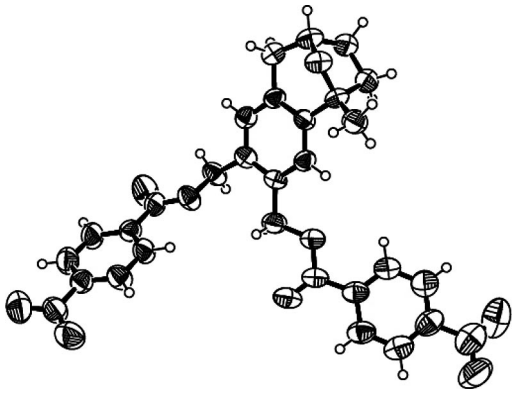


Figure 2. ORTEP diagram of compound **11**.

To illustrate the flexibility of our strategy, various alkynes were employed in the trimerisation reaction with diyne **4** and Wilkinson's catalyst, and the results are summarised in Tables 1 and 2. With simple acetylene (Table 2, Entry 1), the reaction was carried out in a sealed tube and 3,4-benzannulated 8-oxabicyclo[3.2.1]octane (**12**) was obtained in moderate yield. The cyclotrimerisation reaction was attempted with the use of other available symmetrical alkynes such as dimethylacetylene dicarboxylate, bis(trimethylsilyl)-acetylene and diphenylacetylene, but these reactions were unsuccessful (Table 2, Entries 9–11) and self-dimerised products of diyne **4** were formed predominantly.

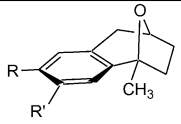
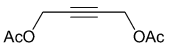
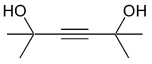
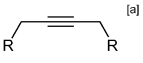
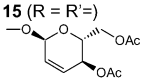
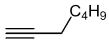
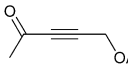
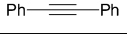
Table 1. Catalysts used for the trimerisation of **4** and **9**.

Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%]
$Ni(cod)_2/PPh_3$	THF/toluene	reflux	10	23
$Mo(CO)_6$	THF/toluene	reflux	12	18
$Rh(PPh_3)_3Cl$	toluene/ethanol	80	3	85
$CoCl_2{\cdot}6H_2O$/L[a]/Zn	THF	reflux	–	–
$[Ir(cod)Cl]_2$dppe	THF/toluene	reflux	–	–

[a] L = 2-(2,6-diisopropylphenyl)iminomethylpyridine.

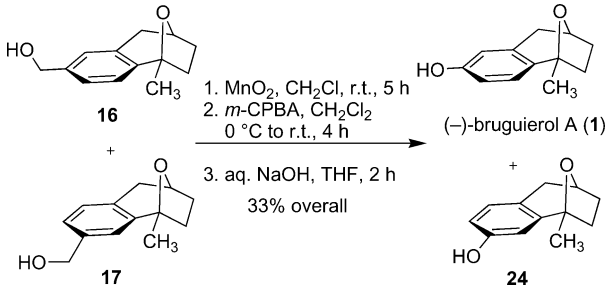
Unsymmetrical alkynes like phenylacetylene, hex-1-yne and propargyl alcohol gave 1:1 inseparable regioisomeric mixtures in moderate-to-good yields. With 1-acetyloxy-2-pentyne-4-one (Table 2, Entry 8), an inseparable 4:1 mixture of regioisomeric products was obtained, and the constitution of the major isomer was deduced with the help of the NOESY spectrum of a mixture of **22**/**23**.

Table 2. Trimerisation of **4** {3 mol-% $[Rh(PPh_3)_3Cl]$, toluene, 80 °C} with different alkynes.

Entry	Alkyne	Yield [%]	Products
			
1		44	**12** (R = R'= -H)
2		72	**13** (R = R'= -CH_2OAc)
3		52	**14** [R = R'= -$C(CH_3)_2OH$]
4	 [a]	54	**15** (R = R'=) 
5		67	**16** (R = H, R'= -CH_2OH) **17** (R = -CH_2OH, R'= -H)
6		82	**18** (R = H, R'= -C_5H_{11}) **19** (R = -C_5H_{11}, R'= -H)
7		59	**20** (R = H, R'= -Ph) **21** (R = -Ph, R'= -H)
8		72	**22** (R = -CH_2OAc, R'= -Ac) **23** (R = -Ac, R'= -CH_2OAc)
9		No reaction	—
10		No reaction	—
11		No reaction	—

[a] For the preparation of this substrate see ref.[19]

After establishing the feasibility of the [2+2+2] cyclotrimerisation reaction for the synthesis of the 3,4-benzannulated 8-oxabicyclo[3.2.1]octane system, we next proceed to the synthesis of bruguierol A by using compounds **16/17**. The elaboration of compounds **16/17** to bruguierol A (**1**) and its regioisomer **24** is summarised in Scheme 3 and Figure 3. Oxidation of the **16/17** mixture with MnO_2 followed by treatment with *m*-CPBA[20] provided bruguierol A (**1**) and **24** in 33% overall yield, and the products were separated and characterised. The spectroscopic data of synthetic bruguierol A (**1**) was in excellent agreement with the data reported for the natural product. In addition, single-crystal X-ray structural analyses of **1** and **24** established their constitution without a doubt.[21] However, the optical rotation of the synthetic sample of **1** {$[\alpha]_D$ = –19.8 (*c* = 1.0, $CHCl_3$)} was similar to the reported value {$[\alpha]_D$ = +14.4 (*c* = 0.3, $CHCl_3$)}[10] but opposite in sign, which indicated that the synthetic sample was the enantiomer of bruguierol A, which established the absolute stereochemistry of bruguierol A as 5*R*,8*S*.



Scheme 3. Synthesis of bruguierol A (**1**) and its isomer **24**.

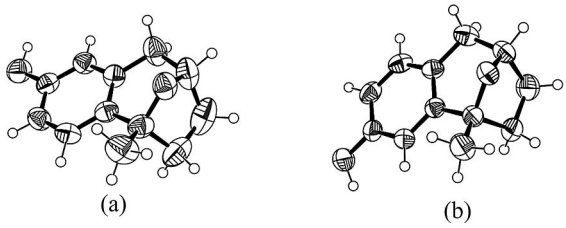


Figure 3. ORTEP structure of (a) bruguierol A (**1**) and (b) **24**.

Conclusions

The chemistry described herein demonstrates the applicability of a rhodium-catalysed [2+2+2] cyclotrimerisation reaction for the construction of 3,4-benzannulated 8-oxabicyclo[3.2.1]octane systems. An expedient total synthesis of bruguierol A (**1**) was completed, and its absolute configuration was established. As a result of the minimal use of protecting groups and the late-stage installation of the key bicyclic system, the present approach leaves ample room for library syntheses. Considering the operational simplicity, this methodology has the potential to be used to gain entry into the synthesis of benzene-fused bridged bicyclic systems, which are prevalent in various natural products and in some of the investigational drugs. Efforts to extend the chemistry described herein to bruguierol B and C and the variation of the central heteroatom to synthesise related natural product like libraries are currently underway in our research group.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterisation data for all compounds.

Acknowledgments

We thank the Director of the National Chemical Laboratory and Dr. M. K. Gurjar (Head, Organic Chemistry Division) for their constant encouragement, and S. R. S. thanks the CSIR (New Delhi) for financial assistance in the form of a research fellowship.

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[21] CCDC-649538 (**1**), -649537 (**11**) and -649539 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: July 16, 2007
Published Online: September 14, 2007

