A general, norbornyl based approach to anti-Bredt alkenes via sequential RCM-fragmentation strategy

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Received (in Cambridge, UK) 15th April 2002, Accepted 16th May 2002
First published as an Advance Article on the web 6th June 2002

A general protocol for the synthesis of bicyclo[3.3.1]frame-
works with bridgehead double bond (anti-Bredt alkenes),
from a common, readily available norbornyl precursor,
involving sequential ring closure metathesis (RCM) and
Wharton fragmentation is outlined.

For several decades now, an assortment of bridgehead olefins
(anti-Bredt alkenes) of which bicyclo[3.3.1]non-1(2)-ene
1a,b and bicyclo[3.2.2]non-1(7)-ene 2c are prototypes, have
been challenging targets of synthesis as these molecules provide
insights into the strain induced distortions about the double
bond and its manifestation in chemical reactivity.1,2 Several
strategies have been recently reported in the literature that provide access to
tertiary hydroxy groups in 9. We have been enticed by
this area and report a new, general approach to bicyclo[n.3.1]frameworks, in the context of the synthesis of taxoids3
and CP molecules4 but general methodologies towards
anti-Bredt alkenes are rather limited.5,6 We have been intrigued by this area and report a new, general approach to bicyclo[n.3.1]framework based bridgehead olefins (anti-Bredt alkenes) which emanates from a norbornyl platform 5 and involves in sequential ring closure metathesis (RCM, 5→6) and Wharton fragmentation (7→8) as the pivotal steps as shown in Scheme 1.

Scheme 1

The key element of the approach delineated in Scheme 1 is the assembly of the norbornyl precursor 5 in which the two alkene arms at C2 and C7 are projected on the exo- and syn-face, respectively, in order to facilitate the RCM to the bridged tricyclic system 6. When the unprotected hydroxy group in 6 is activated as in 7, a facile fragmentation can be expected to deliver bridgehead alkenes 8 with high level of functionalization. Successful execution of this scheme forms the subject matter of this communication.

Our synthetic approach emanated from the keto-acetate 9, a readily available 2,7-disubstituted norbornyl derivative.7 Addi-
tion of vinyl magnesium bromide to 9 did not exhibit significant facial discrimination8 and base hydrolysis furnished anti- and syn-addition products 10 and 11 (45:55), Scheme 2.9 The secondary hydroxy group in syn-11 was oxidised and the tertiary hydroxy group was protected to furnish 12. Further vinylation of the C2 carbonyl in 12 led to a readily separable mixture of endo- and exo-addition products 13 and 14 (58:42).9

The requisite exo-, syn-divinyl compound 14 on exposure to Grubbs’ catalyst [benzylidene-bis(tricyclohexylphosphine)-di- chlororuthenium]10 underwent smooth RCM11 to furnish the tricyclic olefin 18 bearing the brexane framework, Scheme 3. Catalytic hydrogenation of 15 to 16 and mesylation furnished the tricyclic endo-mesylate 17.9 TMS-deprotection to 18 and exposure to base resulted in a smooth fragmentation, as contemplated, to deliver the anti-Bredt bicyclo[3.3.1]non-1(8)-en-4-one 19 in good yield, Scheme 3.

In the backdrop of the successful acquisition of 19, we looked for the generalization of this protocol. Accordingly, the keto-acetate 9 was subjected to allylation under Barbier conditions employing different metals to fine tune face-selectivity and obtain better access to the desired syn isomer 20, Scheme 4.

Allylation in the presence of zinc proved to be the best option with 68:32 ratio of 20 and 21.9 The syn isomer 20 was further elaborated to the TMS-protected ketone 22 through a series of straightforward transformations, Scheme 5. Further allylation of 22 proceeded cleanly but the steric factors dominated the addition to give 23 and 24 (3:1)9 in which the required diastereomer formed through exo-addition was the minor product, Scheme 5. Nonetheless, 24 underwent smooth RCM in the presence of the Grubbs’ catalyst18 to furnish the tricycle 25.
Scheme 3. Reagents and conditions: Grubbs’ catalyst (30 mol%), C₂H₅Br, reflux, 83%; (ii) 10% Pd/C, H₂, EtOAc, 95%; (iii) MsCl, Et₃N, DMAP, DCM, 0 °C, 85%; (iv) TBAF, THF, rt, 80%; (v) MsCl, Et₃N, DMAP, DCM, 0 °C, 87%.

Scheme 4. Reagents and conditions: (i) K₂CO₃, MeOH, rt, 78%; (ii) PCC, C₂H₅OH, rt, 76%; (iii) MsCl, Et₃N, DMAP, DCM, 0 °C, 85%.

Scheme 5. Under the conditions of mesylation, 25 underwent rapid fragmentation to yield bicyclo[5.3.1]undeca-1(10),3-dien-6-one 26. Scheme 5. The skeleton of the bridgehead alkene 26 is reminiscent of the bicyclic AB ring core of taxoids.

Our last example is of access to the bicyclo[4.3.1]dec-2(9)-ene 34. Vinylation of 22 was again dominated by steric considerations and furnished endo- and exo-addition products 27 and 28 (73:27). The exo, syn-28 readily underwent RCM in the presence of Grubbs’ catalyst 30 to furnish the tricyclic olefin 29. Scheme 6. As the direct fragmentation on 29 was unsuccessful, perhaps due to strain factors, the double bond in it was reduced to furnish 30. Exposure of 30 to methanesulfonyl chloride in the presence of base resulted in fragmentation to furnish bicyclo[4.3.1]dec-2(9)-en-5-one 9.

Notes and references
9 All new compounds reported here were duly characterized on the basis of spectroscopic data and elemental analyses. Diastereomers 13/14, 20/21, 23/24 and 27/28 were all separated through chromatography on a SiO₂-gel column.