Pergamon

Tetrahedron Letters 42 (2001) 3013–3015

TETRAHEDRON LETTERS

Synthesis of the azatricyclic core of FR901483 by bridgehead vinylation via an anti-Bredt iminium ion

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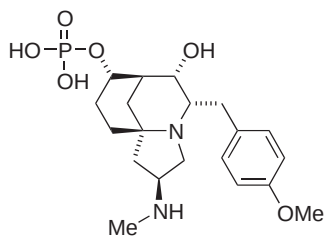
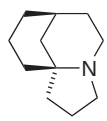
Received 20 December 2000; revised 8 February 2001; accepted 23 February 2001

Abstract—We have developed an alternative route to the azatricyclic core skeleton of FR901483 based on vinylation at the bridgehead position of 2-azabicyclo[3.3.1]nonane via an anti-Bredt iminium ion using vinylaluminum reagents.

FR901483 (**1**) isolated from the fermentation broth of *Cladobotryum* sp. No. 11231 by the Fujisawa group[1] is a new immunosuppressant containing a novel 5-azatricyclo[6.3.1.0^{1,5}]dodecane ring system. Significant biological activity and unique chemical structure couple to make **1** an attractive target for total synthesis. In view of the structural feature, the synthetic approach requires an efficient method for the construction of the azatricyclic framework, which has recently been achieved based on an approach involving a nitrone cycloaddition and aldol condensation by Snider,[2] leading to the first total synthesis of FR901483. In the previous year, we have shown[3] the viability of a new approach based on nucleophilic bridgehead alkylation on an 'anti-Bredt iminium ion' for the construction of the azatricyclic core **2** of **1**. As a continuation of our studies in this field, we have undertaken the investigation of the application of this methodology to an efficient synthesis of this core structure. In this paper, we now report development of an alternative route to 5-azatricyclo[6.3.1.0^{1,5}]dodecane (**2**) based on vinylation using trivinylaluminum at the bridgehead position of the anti-Bredt iminium ion.

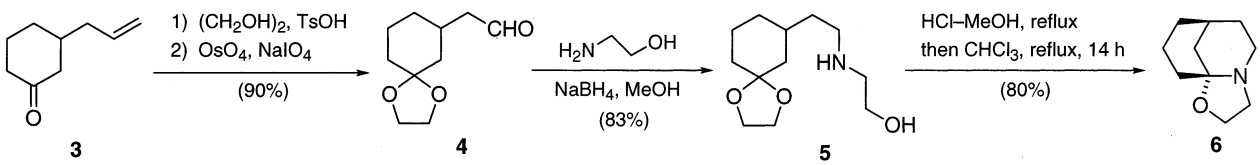


FR901483 (**1**)



2

Ketalization of **3** and oxidative cleavage of the olefin moiety gave the aldehyde **4**, which was converted to the secondary amine **5** via Schiff base formation with ethanolamine followed by reduction with $NaBH_4$ in methanol. After removal of the ketal group of **5** by acid treatment, a chloroform solution of the resulting keto-amino alcohol was refluxed to form the tricyclic oxazolidine **6** in 80% yield (Scheme 1).



3 **4** **5** **6**

Scheme 1.

Keywords: bridgehead chemistry; metathesis; oxazolidines; vinylation.

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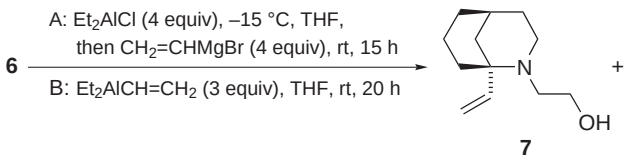
PII: S0040-4039(01)00345-8



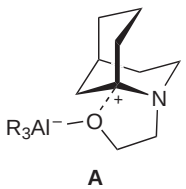
	yield, %		
	7	**8**	**6** recovered
method A	20	19	52
method B	69	13	16

Scheme 2.

In a first attempt to effect bridgehead vinylation of **6**, a mixture of **6** and 2 equiv. of Et_2AlCl in THF was stirred at −15°C for 5 min, and to this was added 2 equiv. of vinylmagnesium bromide in THF and the mixture was stirred at room temperature according to our previously reported procedure[3] for the Lewis acid-mediated bridgehead alkylation; this, however, resulted in no reaction with recovering starting material. When 4 equiv. of Et_2AlCl and vinyl magnesium bromide were employed under similar reaction conditions, the desired 1-vinylated azabicyclononane **7** was obtained, however, with the poor yield (20%) and accompanying the formation of the 1-ethylated product **8** in 19% yield with recovery of the starting material (52%) (method A in Scheme 2). We noted that the use of diethylvinylalane, $Et_2AlCH{=}CH_2$, prepared in advance by reacting Et_2AlCl (3 equiv.) with vinylmagnesium bromide (3 equiv.) in THF, led to a significant improvement of the yield of **7** (69%), together with the ethylated product **8** (13%) and unreacted starting material (16%) (method B in Scheme 2).

To eliminate such vinylation versus ethylation competition in the nucleophilic substitution at the bridgehead position using the mixed alane such as $Et_2AlCH{=}CH_2$, we next decided to examine the use of R_3Al as the nucleophile which behaves, at the same time, as the Lewis acid.[4] Thus, $(CH_2{=}CH)_3Al$,[5] prepared in situ from $AlCl_3$ (2 equiv.) and vinylmagnesium bromide (6 equiv.) in Et_2O, was allowed to react with the tricyclic oxazolidine **6** at room temperature to afford the only vinylated product **7** in 67% yield, but the reaction required a long reaction time (22 h) in order to reach completion (Table 1, entry 1). The use of 3 equiv. of $(CH_2{=}CH)_3Al$ in THF greatly enhanced the reaction rate (3 h); however, the product yield of **7** was found to be lower (entry 2). The best result was obtained using 3 equiv. of $(CH_2{=}CH)_3Al$ in Et_2O as the solvent (rt, 4 h), which afforded **7** in 93% yield (entry 3). Similar treatment with $(CH_3CH{=}CH)_3Al$ (1:1 *E*/*Z* mixture), prepared from 1-propenylmagnesium bromide (1:1 *E*/*Z* mixture) and $AlCl_3$, and (E)-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$, prepared by hydroalumination of 1-heptyne with DIBALH, resulted in the corresponding bridgehead alkenyl-substituted azabicyclononanes **9** (88%) and **10** (65%), respectively, as a single product in either case (entries 4 and 5). Bridgehead substitution was also effected by means of Ph_3Al[6] and $(C_5H_{11}C{\equiv}C)_3Al$[7] to give the 1-phenylated and 1-alkynylated azabicyclononanes **11** and **12**, respectively (entries 6 and 7).

These results obtained by using R_3Al can be interpreted, in agreement with those reported previously by us,[3] in terms of initial complexation of R_3Al to the oxygen atom in the oxazolidine moiety of **6** leading to C–O bond breaking to form a bridgehead carbocation **A**, which facilitates generation of the intermediacy bridgehead iminium ion **B**. Subsequent nucleophilic attack of another molecule of R_3Al may occur exclusively at the bridgehead position to form the 1-substituted azabicyclononanes.



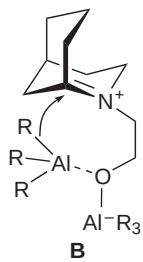
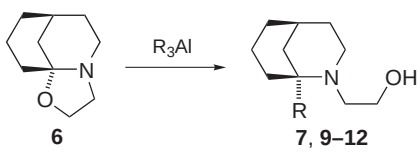
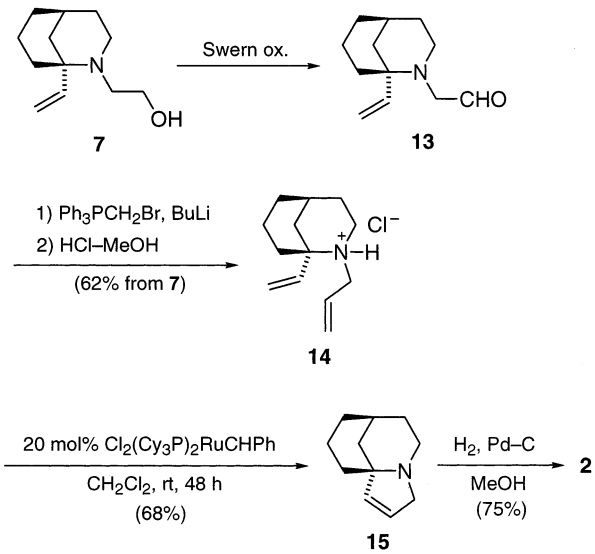


Table 1. Nucleophilic C–C bond formation with aluminum reagents



Entry	Aluminum reagent (equiv.)	Solvent	Time (h)[a]	Product	Yield (%)[b]
1	$(CH_2{=}CH)_3Al$ (2)	Et_2O	22	**7**: R = CH=CH_2	67
2	$(CH_2{=}CH)_3Al$ (3)	THF	3	**7**: R = CH=CH_2	51
3	$(CH_2{=}CH)_3Al$ (3)	Et_2O	4	**7**: R = CH=CH_2	93
4	$(CH_3CH{=}CH)_3Al$ (*E*/*Z* 1:1) (3)	Et_2O	7	**9**: R = CH=$CHCH_3$ (*E*/*Z* 1:1)	88
5	(E)-$C_5H_{11}CH{=}CHAl(i\text{-}Bu)_2$ (3)	Et_2O	3	**10**: R = (E)-CH=CHC_5H_{11}	65
6	Ph_3Al (3)	Et_2O	2	**11**: R = Ph	89
7	$(C_5H_{11}C{\equiv}C)_3Al$ (3)	Et_2O	1	**12**: R = C≡CC_5H_{11}	88

[a] The time at which the starting material disappeared by TLC monitoring.
[b] Isolated yield after chromatographic purification.



Scheme 3.

The bridgehead-vinylated azabicyclononane **7** obtained was then subjected to Swern oxidation to give the aldehyde **13**, which was converted to the amino diene hydrochloride salt **14** (mp 170–172°C) by Wittig olefination followed by treatment with HCl–MeOH. Five-membered ring construction was efficiently achieved by application of ring-closing olefin metathesis[8] to **14** with 20 mol% of Grubbs' catalyst[9] in CH_2Cl_2 at room temperature to furnish the azatricyclododecene **15** in 68% yield, though the olefin metathesis using the free base of **14** did not proceed under these conditions.[10] Hydrogenation over Pd–C converted **15** to **2** (75% yield) and this material proved to be identical in all respects with an authentic sample prepared previously by us (Scheme 3).[3]

In conclusion, we have developed an alternative route to the azatricyclic core skeleton of FR901483 based on vinylation at the bridgehead position of the 2-azabicyclo[3.3.1]nonane ring via the anti-Bredt iminium ion using the trivinylaluminum reagent.

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