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Concise enantioselective construction of a bridged azatricyclic framework *via* domino semipinacol–Schmidt reaction†

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A $TiCl_4$-promoted domino semipinacol–Schmidt reaction of oxaspiropentane-azide provides an easy access to bridged azatricyclic ring systems, which possess the azaquaternary center, present in the immunosupressant FR901483 and platelet aggregation inhibitor daphlongeranine B.

A number of alkaloids possessing linearly and angularly fused as well as the bridged aza-polycyclic frameworks are widespread in nature (Fig. 1).[1–3] The stemoamide family of alkaloids possess a linearly fused aza-polycyclic framework, whereas angularly fused aza-polycyclic ring systems are widespread in the family of stenine and stemonamine alkaloids.[1] Likewise, structurally diverse bridged aza-polycyclic ring systems are very common in *Daphniphyllum*[2] and *Lycopodium*[3] alkaloids. In recent years, biologically significant alkaloids bearing an intriguing bridged azatricyclic core coupled with the presence of an azaquaternary center have evoked considerable interest among the synthetic chemists.[4,5]

The immunosuppressant FR901483 (**1**) possesses an unusually novel bridged azatricyclic skeleton formed by the spiro fusion of the morphan structural motif (2-azabicyclo[3.3.1]nonane) and pyrrolidine ring (Fig. 2). As a consequence of its potent biological activity and remarkable structural framework, a number of approaches towards the synthesis of FR901483 (**1**) as well as its bridged azatricyclic core, 5-azatricyclo[6.3.1.$0^{1,5}$]dodecane, have been reported.[6,7] Similarly, daphlongeranine B (**2**), a member of the *Daphniphyllum* alkaloids, is a novel platelet aggregation inhibitor having an unprecedented bridged hexacyclic framework coupled with an azaquaternary center whose synthesis has not been realized so far.[8]

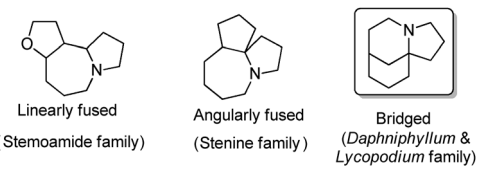

Fig. 1 Prevalent aza-structural motifs present in natural products.

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† Electronic supplementary information (ESI) available: Representative experimental procedure and characterization of reaction products. CCDC 840274. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31906c

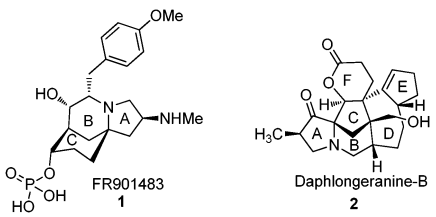
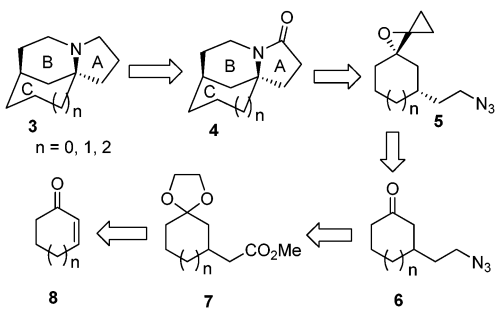


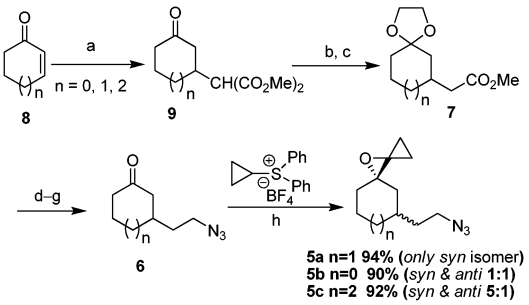
Fig. 2 Biologically active alkaloids having a bridged azatricyclic core coupled with an azaquaternary center.

Several synthetic approaches for the construction of linearly[9] as well as angularly fused azatricyclic ring systems containing an azaquaternary center have been reported, which include a semipinacol–Schmidt based rearrangement,[10a] a tandem Prins–Schmidt cyclization,[10b] and a nitrone based intramolecular dipolar cycloaddition,[10c] however the stereoselective construction of a bridged azatricyclic system having an azaquaternary center is synthetically quite demanding and only a few methods have been devised to achieve this structural motif which includes sequential formal [4 + 3] cycloaddition followed by stereocontrolled enolate chemistry,[5a] an enoxysilane *N*-sulfonyliminium ion cyclization,[5b] and highly diastereoselective formal [3 + 3] cycloaddition followed by transannular Mannich reaction.[5c]

Herein, we report an exceptionally simple and efficient approach for the construction of a bridged azatricyclic ABC-core of FR901483 (**1**) and daphlongeranine B (**2**) using domino semipinacol–Schmidt cyclization as a key step.[11–13] The retrosynthetic analysis is shown in Scheme 1. Oxaspiropentane-azide **5**, a key intermediate in the domino semipinacol–Schmidt cyclization reaction, can be readily synthesized using the Trost spiroannelation[14] protocol from the corresponding azido-ketone **6**,



Scheme 1 Retrosynthetic analysis of a bridged azatricyclic ABC-core of alkaloids **1** and **2**.

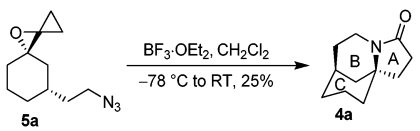


Scheme 2 Synthesis of oxaspiropentane-azide **5**. Reagents: (a) $CH_2(CO_2Me)_2$, K-O^{t}Bu, THF, RT, 92–95%; (b) $(CH_2OH)_2$, PTSA, toluene, reflux; (c) NaCl–DMSO, 145 °C, 62–65% over two steps; (d) $LiAlH_4$, THF, RT; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C; (f) NaN_3, DMF, 65 °C; (g) PPTS, acetone–H_2O reflux, 48–50% over four steps; (h) ylide, KOH, DMSO, 25 °C, 90–94%.

which in turn can be prepared in a few steps starting from cycloalkenone **8** (Scheme 2).

Azido-ketone **6a** was stereoselectively converted to the corresponding *syn*-oxaspiropentane-azide **5a** in excellent yield as a single diastereomer using the Trost spiroannelation reaction. Under similar reaction conditions, azido-ketone **6b** gave a 1 : 1 inseparable mixture of *syn*- and *anti*-oxaspiropentane-azide **5b** in 90% yield, whereas azido-ketone **6c** furnished a 5 : 1 mixture of *syn*- and *anti*-oxaspiropentane-azide **5c**, respectively, in 92% yield (Scheme 2).

When exposed to $BF_3{\cdot}OEt_2$, the *syn*-oxaspiropentane-azide **5a** in DCM at −78 °C underwent domino semipinacol–Schmidt rearrangement to give the corresponding bridged azatricyclic lactam **4a** in 25% yield (Scheme 3).



Scheme 3 Domino semipinacol–Schmidt reaction of *syn*-oxaspiropentane-azide **5a**.

Encouraged by this preliminary observation, this novel cyclization was carried out with different Lewis acids and the results obtained are summarized in Table 1.

Among the Lewis acids screened, $TiCl_4$ was found to be the most efficient catalyst to bring about this domino transformation and furnished the corresponding bridged azatricyclic ABC-core **4a** of immunosuppressant FR901483 (**1**) in a stereoselective manner, which on subsequent reduction with $LiAlH_4$ furnished the known bridged azatricyclic system **3a**, whose mass and NMR spectral data are found to be in complete agreement with the literature values.[7a] Similarly, the mixture of *syn*- and *anti*-oxaspiropentane-azide **5b** on exposure to $TiCl_4$ resulted in the corresponding bridged azatricyclic ABC-core **4b** of daphlongeranine B (**2**) in 80% yield, based on the *syn*-isomer (Table 2).[15] The structure and the relative stereochemistry of the cyclized product **4b** was unambiguously confirmed by single crystal X-ray analysis of the corresponding thiolactam derivative (±)-**10b** (Fig. 3). Interestingly, this is the first stereoselective approach for the construction of the bridged azatricyclic ABC-core of daphlongeranine B (**2**). Under similar cyclization conditions, the *syn*- and *anti*-mixture of oxaspiropentane-azide **5c** afforded the corresponding bridged azatricyclic lactam **4c** in 80% yield based on the *syn*-isomer. Reduction of cyclized azatricyclic lactams **4b** and **4c** afforded the corresponding bridged azatricyclic amines **3b** and **3c**, respectively, in excellent yields (Table 2).

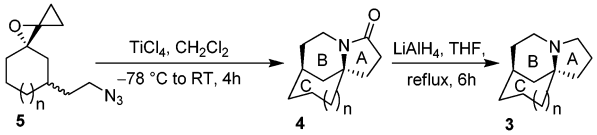
The scope of this novel stereoselective transformation was further explored in the enantioselective construction of the bridged azatricyclic ABC-core of FR901483. The asymmetric

Table 1 Domino semipinacol–Schmidt reaction of *syn*-oxaspiropentane-azide **5a** with different Lewis acids[a]

Entry	Lewis acid	Time/h	Yield of **4a**[b] (%)
1	TMSOTf	4	59
2	$EtAlCl_2$	6	62
3	$TiCl_4$	4	78

[a] Reactions were performed using 2.5 equiv. of Lewis acid. [b] Isolated yield.

Table 2 $TiCl_4$-promoted domino semipinacol–Schmidt reaction of oxaspiropentane-azide **5**[a]



Entry	Oxaspiro pentane-azide **5**	Ratio of **5**[b] (*syn*/*anti*)	Azatricyclic lactam **4**[c] (% yield)	Azatricyclic amine **3**[c] (% yield)
1	**5a** n = 1	1 : 0	**4a** (78)	**3a** (94)
2	**5b** n = 0	1 : 1	**4b** (80)[d]	**3b** (92)
3	**5c** n = 2	5 : 1	**4c** (80)[d]	**3c** (94)

[a] Reactions were performed using 2.5 equiv. of $TiCl_4$. [b] *Syn*- and *anti*-mixture was used in the reaction. [c] Yield is shown in parentheses. [d] Isolated yield based on the *syn*-isomer.

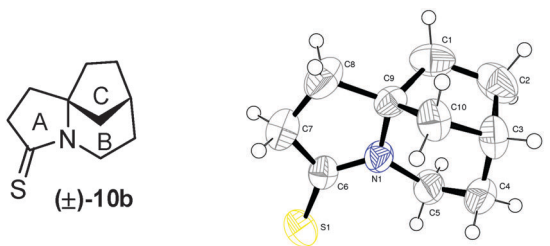
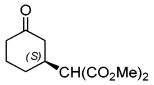
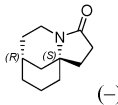
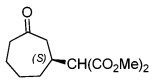
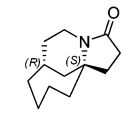
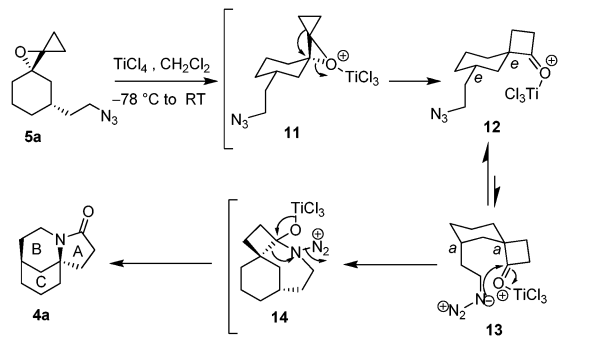


Fig. 3 ORTEP-diagram of thiolactam derivative (±)-**10b** of the ABC ring system of daphlongeranine B.

Table 3 Enantioselective synthesis of the bridged azatricyclic system

S. no.	Michael adduct **9**	ee[a] (%)	Azatricyclic lactam **4**[b]	ee[a] (%)
1	 (−)-**9a** $[\alpha]^{25}_{D}$ −3.4 (*c* 0.1, $CHCl_3$)	99	 (−)-**4a** $[\alpha]^{26}_{D}$ −38.0 (*c* 1.0, $CHCl_3$)	99
2	 (−)-**9c** $[\alpha]^{25}_{D}$ −41.0 (*c* 1.0, $CHCl_3$)	99	 (−)-**4c** $[\alpha]^{23}_{D}$ −32.0 (*c* 1.0, $CHCl_3$)	99

[a] % ee calculated using chiral HPLC. [b] HPLC analysis was done on the corresponding thiolactam derivative.



Scheme 4 Plausible mechanism for the domino semipinacol–Schmidt reaction of *syn*-oxaspiropentane-azide.

Michael addition of dimethyl malonate with cyclohexenone and cycloheptenone in the presence of Shibasaki (*S*)-ALB catalyst[16] furnished the corresponding adducts (−)-**9a** and (−)-**9c**, respectively, in 99% ee. Following a similar sequence of reactions as shown in Scheme 2, the Michael adducts were further converted to the azatricyclic lactam (−)-**4a** and (−)-**4c**, respectively, in good yields (Table 3). The azatricyclic lactam (−)-**4a** is the enantiomer of the ABC core of FR901483.[17]

A plausible mechanism for the formation of a bridged azatricyclic framework from *syn*-oxaspiropentane-azide **5** *via* domino semipinacol–Schmidt cyclization is depicted in Scheme 4.

In summary, a novel and general approach for the stereo- and enantioselective construction of bridged azatricyclic ring systems having an azaquaternary center has been developed based on a domino semipinacol–Schmidt reaction. This new method has provided an elegant entry for the compact synthesis of the ABC-core of the biologically significant alkaloids such as FR901483 and daphlongeranine B. Since our approach is simple and effective, it can be readily implemented in the stereo- and enantioselective synthesis of natural products possessing bridged aza-polycyclic frameworks.

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