Highly efficient construction of an oxa-[3.2.1] octane-embedded 5–7–6 tricyclic carbon skeleton and ring-opening of the bridged ring via C–O bond cleavage†‡

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We report herein a highly efficient strategy for construction of a bridged oxa-[3.2.1]octane-embedded 5–7–6 tricyclic carbon skeleton through [3 + 2] IMCC (intramolecular [3 + 2] cross-cycloaddition), and the substituents and/or stereochemistries on C-4, C-6, C-7 and C-10 fully match those in the rhamnofolane, tigliane and daphnane diterpenoids. Furthermore, ring-opening of the bridged oxa-[3.2.1]octane via C–O bond cleavage was also successfully achieved.

Rhamnofolane, tigliane, and daphnane are three families of diterpenoids displaying a broad range of biological activities such as antiviral, anticancer, anti-HIV, immunomodulatory and neurotrophic activities. Three representative members are neoglабrescin A and curcusones IJ. The unique structural features of these three compounds include a 5–7–6 tricyclic carbon skeleton with a trans-fused 5–7 bicyclic skeleton, a 4,7-bridged oxa-[3.2.1]octane skeleton and a methylene (methyl) group at C-6 (Fig. 1). Some other related natural products include crotophorbole, phorbol, prostratin, resiniferatoxin and curcusone A.

Due to their remarkable biological activities and unique and complex structures, these types of diterpenoids have drawn considerable attention from organic chemists, and many creative strategies have been developed for construction of the 5–7–6 tricycles with desirable substituents and stereochemistries on C-4, C-6, C-7 and C-10. Dai et al. reported the total syntheses of curcusones I and J by using an intramolecular Au-catalysed [4 + 3] cycloaddition for construction of the oxa-[3.2.1]octane skeleton and a methylene (methyl) group at C-6 (Scheme 1). Some other related natural products have been reported by the groups of Wender (phorbol, resiniferatoxin and prostratin), Cha (phorbol), Baran (phorbol), Xu/Li (prostratin), Liu (crotophorbole), Inoue (crotophorbole, resiniferatoxin, prostratin and related molecules) and Dai/Adibekian (curcusones A–D). The groups of West and Maimone have reported attempts toward the total syntheses of related molecules through construction of a 4,7-bridged oxa-[3.2.1]octane skeleton respectively (Scheme 2).
We have previously reported a highly efficient construction of 5–7–6 tricyclic carbon skeleton with an intramolecular \([4 + 3]\) IMPC (intramolecular \([4 + 3]\) parallel-cycloaddition) of cyclopropane with dendralene/Diels–Alder \([4 + 2]\) cycloaddition strategy.\(^{17}\) With this strategy, the fused 5–7 bicyclic skeleton was efficiently constructed which matched the trans-stereochemistry, however a C-4 oxygen atom was not be direct.

Following our previously developed \([3 + 2]\) IMCC strategy,\(^{18}\) we have recently reported a novel and efficient construction of a bridged aza-[3.2.1]octane-embedded 5–7–6 tricyclic carbon skeleton with desirable substituents and stereochemistries toward total syntheses of calycinaphyline D-type \textit{Daphniphyllum} alkaloids (Scheme 3).\(^{19}\) Herein, we report the application of the \([3 + 2]\) IMCC strategy for efficient construction of the bridged oxa-[3.2.1]octane-embedded 5–7–6 tricycle with stereochemistries on C-4, C-6, C-7 and C-10, as well as a methylene (methyl) group at C-6 matching those in neoglubrescin A, curcusones I/J and related rhamnofolane/tigliane/daphnane diterpenes.

We started the research from benzyl bromide 2 which was prepared from a known compound 1 according to our recently reported method (Scheme 4).\(^{18}\) Compound 2 was then oxidized with NMO to a form aldehyde 3 which was used directly in the next step without further purification. Under catalysis of Sc(OTf)\(_3\) (0.2 equiv.), the \([3 + 2]\) IMCC of aldehyde 3 was successfully carried out to afford compound 4 in 82% yield over two steps. The structure of 4 was confirmed by X-ray crystal structure analysis.\(^{19}\) Hereeto, the bridged oxa-[3.2.1]octane-embedded 5–7–6 tricycle have been successfully constructed, the substituents and stereochemistries on C-4, C-6, C-7 and C-10 fully match those in the corresponding natural products.

With compound 4 in hand, we started to investigate the ring-opening of the bridged oxa-[3.2.1]octane \textit{via} C-O bond cleavage (Scheme 5). Krapcho decarboxylation of 4 afforded monoester 5 in 88% yield as a mixture of two diastereoisomers in a ratio of nearly 1 : 1. Reduction of 5 with DIBAL-H at \(-78\,^\circ\text{C}\) afforded...
aldehyde 6 in 85% yield. To our delight, the oxa-bridge was opened under catalysis of TMSOTf at $-5^\circ C$ and a dehydration product 7 was obtained in 16% yield (brsm 53%) (Table 1, entry 1). Unfortunately, we failed to obtain compound 9 in several attempts either under acidic or basic conditions (Table 1, entries 2–8).

We have also explored the ring-opening of compound 5 under several conditions (Table 2). Both basic condition and single electron transfer reduction could not give 10a (Table 2, entries 1–3). Fortunately, we found that treatment of 5 with acetic toluene-\(p\)-sulfonic anhydride afforded compound 8 in 98% yield, as a mixture of two diastereoisomers (Table 2, entry 4). The ratio of the trans/cis-isomers was 3 : 2 which could be confirmed with \(^1H\) NMR and density functional theory (DFT) calculations (see ESI†). During the synthesis of viridin, Akai et al. found that the ring-opening product of a similar oxa-bridged compound was unstable. Methylation of the resultant oxyanion \textit{in situ} with MeOTf gave a more stable product. However, we failed to get 10b by using this method (Table 2, entries 5 and 6).

In conclusion, we have developed a highly efficient strategy for construction of the bridged oxa-[3.2.1]octane-embedded 5–7–6 tricyclic carbon skeleton through the [3 + 2] IMCC, the substituents and stereochemistries on C-4, C-6, C-7 and C-10 fully match those in the corresponding natural products. Furthermore, the ring-opening of the bridged oxa-[3.2.1]octane via C–O bond cleavage was also successfully achieved. We strongly believe that this study will provide a novel and efficient strategy toward the total syntheses of related rhamnofolane, tigliane and daphnane diterpenoids.

| Entry | Solvent | Temperature | Reagents | Yield |
|-------|---------|-------------|----------|-------|
| 1     | DCM     | $-5^\circ C$| TMSOTf   | 7, 16% |
| 2     | DCM     | r.t.       | TMSOTf, Et$_3$N | n.r. |
| 3     | DCM     | $-78^\circ C$ to $-10^\circ C$ | TMSOTf | Complex |
| 4     | MeOH    | r.t. ~ reflux | NaOMe | n.r. |
| 5     | THF     | $-78^\circ C$ | LDA | n.r. |
| 6     | THF     | 0°C | LDA | Complex |
| 7     | THF     | 0°C | DIBAL-H | Decom. |
| 8     | DCM     | 0°C | TIPSOTf | n.r. |

**Scheme 4** Construction of the bridged oxa-[3.2.1]octane-embedded 5–7–6 tricycle.

**Scheme 5** Ring-opening of the oxa-[3.2.1]octane via C–O bond cleavage.

**Table 1** Ring-opening of the compound 6
Table 2  Ring-opening of the compound 5

| Entry | Solvent | Temperature | Reagents | Yield |
|-------|---------|-------------|----------|-------|
| 1     | THF     | 0 °C        | LDA      | Decom. |
| 2     | DME     | r.t.        | Li, EDA  | Decom. |
| 3     | DME     | 0 °C        | Li, EDA  | Decom. |
| 4     | CH$_2$CN | r.t.        | Anhydride$^a$ | Decom. |
| 5     | THF     | –78 °C to 0 °C | LHMDS, MeOTf | 8, 98% (trans : cis = 3 : 2) |
| 6     | THF     | –78 °C to 0 °C | LDA, MeOTf | Decom. |

$^a$ Ethylenediamine. $^b$ Acetonic toluene-$p$-sulfonic anhydride, prepared by acetyl chloride and PTSA.$^{25}$

Conflicts of interest

There are no conflicts to declare.

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19 CCDC 2110705 (4) contain the supplementary crystallographic data for this paper. ORTEP drawings of 4 can be found in the ESI.

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