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Asymmetric synthesis of ABC tricyclic core in *Daphniphyllum* alkaloid 21-deoxy-macropodumine D

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ABSTRACT

In this paper, we describe our efforts toward the asymmetric synthesis of *Daphniphyllum* alkaloid 21-deoxymacropodumine D which led to efficient preparation of a ABC tricyclic framework containing five consecutive stereocenters. This synthetic work features (1) utilization of an asymmetric conjugate addition to install the C5 all-carbon quaternary center, (2) an intramolecular *aza*-Michael addition followed by Pd-catalyzed α-alkenylation to build the bowl-shaped tricyclic core.

Daphniphyllum alkaloids, isolated from the genus *Daphniphyllum*, are a large group of polycyclic natural products containing over 320 members with more than 20 different skeletal types.[1] Many members of this family have showed a wide range of biological activities, including anticancer, antioxidation, antiviral, vasorelaxation, nerve growth factor- regulation, anti-HIV and anti-platelet activating factor effects.[1c,2,3] These significant bioactivities, in combination with intriguing architectural features of *Daphniphyllum* alkaloids, have rendered this family of natural products an alluring target for synthetic chemists.[1,2] In the synthesis campaigns toward these alkaloids, Heathcock and co-workers reported the inaugural elegant works.[4] Subsequently, several total syntheses of *Daphniphyllum* alkaloids were accomplished successively by the groups of Carreira,[5] Smith,[6] Li,[7] Yokoshima/Fukuyama,[8] Zhai[9] and Paton/Dixon.[10]

In this family, the calyciphylline A-type alkaloids are among the most studied members.[1,7–12] Most of this subfamily feature a complex scaffold containing a highly fused 6-6-5-7-5-5 hexacyclic core[1b] (**4**–**6**, Fig. 1). However, daphenylline (**8**, Fig. 1) is a nonrepresentative member possessing a fused 6-6-5-7-5-6 hexacyclic arene-containing skeleton.[7–9,12] Additionally, macropodumine D (**9**, Fig. 1) is another structurally exceptive member in this subfamily, which was isolated from the leaves and barks of *Daphniphyllum* macropodum Miq. by Guo and co-workers in 2007.[13] Recently, its deoxidized congener 21-deoxymacropodumine D (**10**, Fig. 1) was disclosed by the group of Yue,[14] the structure of which was confirmed unambiguously by X-ray diffraction analysis. Structurally, macropodumine D (**9**) and 21-deoxymacropodumine D (**10**) possess an unprecedented 6-5-6-7-5-5 hexacyclic system, and the moiety of rings A, B, and C in particular features a unique fusion of 6-5-6 tricyclic unit, containing the especial *N*-C3 linkage and a hydroxyl group at C4, which is unusual in normal calyciphylline A-type alkaloids (most members have *N*-C4 linkage). The unique scaffold of **9** and **10**, and seven consecutive stereocenters including the vicinal all-carbon quaternary centers pose a challenge for chemical synthesis. Herein, we report our endeavors that led to the asymmetric synthesis of ABC tricyclic framework of 21-deoxymacropodumine D (**10**).

Our retrosynthetic analysis is briefly illustrated in Scheme 1. Application of a late-stage transannular alkylation to hexacyclic framework of 21-deoxymacropodumine D (**10**) led back to primary iodide **11**. We envisioned that the E ring in **11** could be readily prepared from **12** via a SmI_2-promoted ketyl-olefin radical cyclization[15] and subsequent elimination. Formation of the latter spiro intermediate would rely on an intramolecular Aldol strategy of **13**, which in turn could be simplified as ABC tricyclic core **14**. To provide an efficient access to this key tricyclic structure, we

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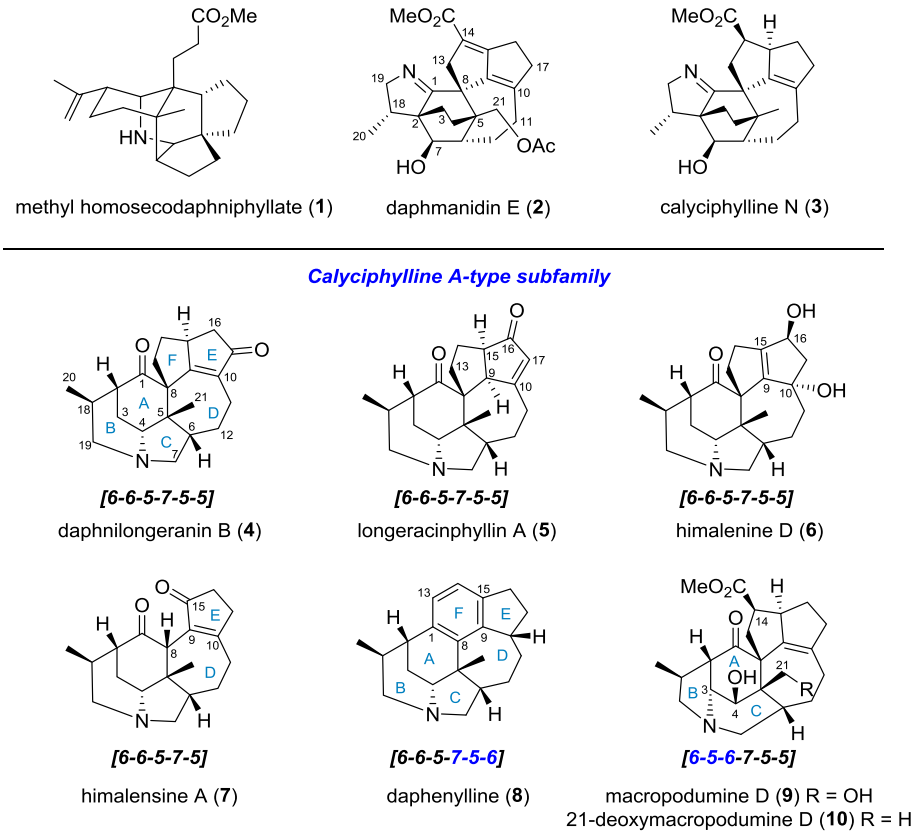
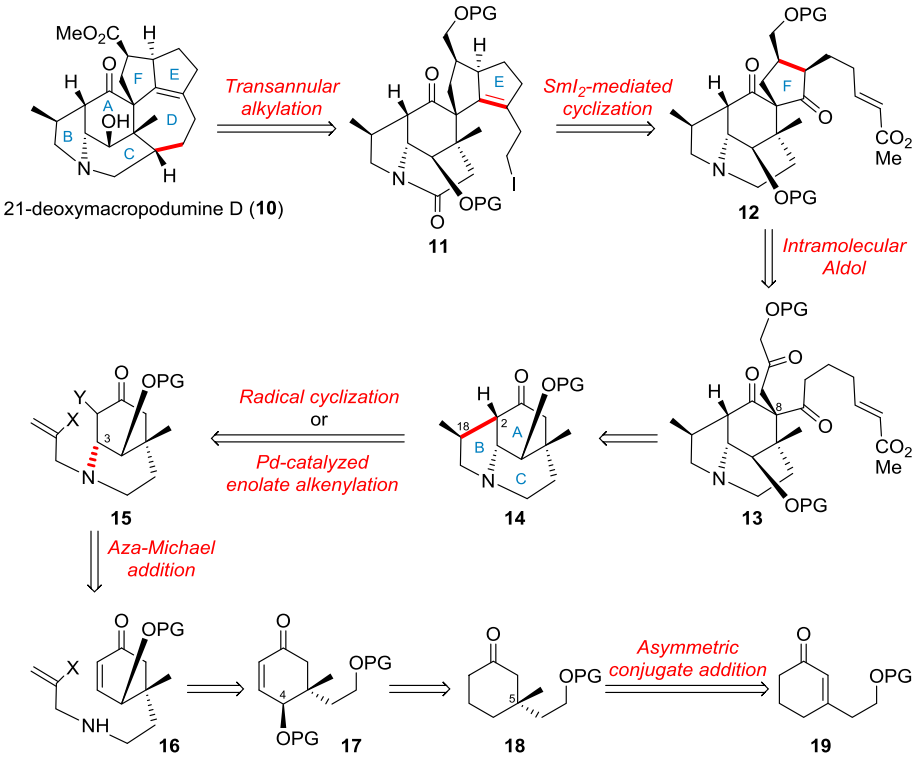


Fig. 1. Selected *Daphniphyllum* alkaloids.



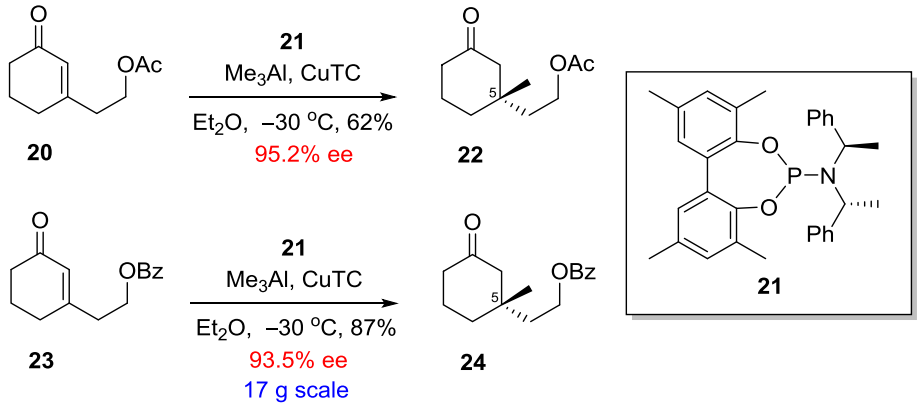
Scheme 1. Retrosynthetic analysis of 21-deoxymacropodumine D (**10**). PG = protecting group.

conceived a radical cyclization[16] (when X = H, Y = PhSe), or an alternative Pd-catalyzed enolate α-alkenylation[11a,11l] (when X = Br, Y = H)/hydrogenation sequence of **15** to forge C2–C18 bond, in which *N*-C3 linkage could be established by an intramolecular *aza*-Michael addition of enone **16**. In turn, introduction of the nitrogen functionality could be achieved through primary alcohol

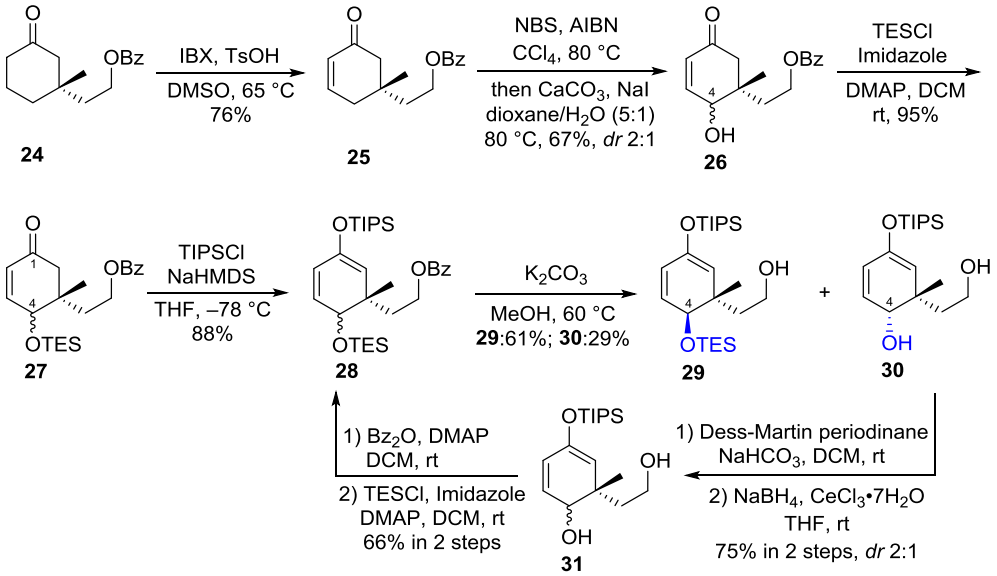
deprotection of **17**, followed by oxidation/reductive amination or Mitsunobu reaction. 17 was traced back to an enantioenriched precursor such as **18**, a compound which could arise from readily available enone **19** via an asymmetric conjugate addition[17] to build the all-carbon quaternary center at C5.

The synthesis commenced with the preparation of enantioenriched ketone intermediate containing C5 all-carbon quaternary center (Scheme 2). Following the copper-catalyzed asymmetric conjugate addition established by Alexakis and co-workers,[17] we were pleased to observe that the reaction of the known α, β-unsaturated ketone **20**[18] using ligand **21** in the presence of Me_3-Al and CuTC in Et_2O at −30 °C smoothly afforded the desired adduct **22** in 62% yield and excellent enantioselectivity up to 95.2% ee. Under the same conditions, the asymmetric conjugate addition of Bz substrate **23** (see Supplementary material) was performed more efficiently (87% yield), delivering **24** in 93.5% ee. Although the enantioselectivity was slightly decreased, this transformation has proven to be scalable (17 g scale), and provided enough material supplies for the subsequent synthetic investigations.

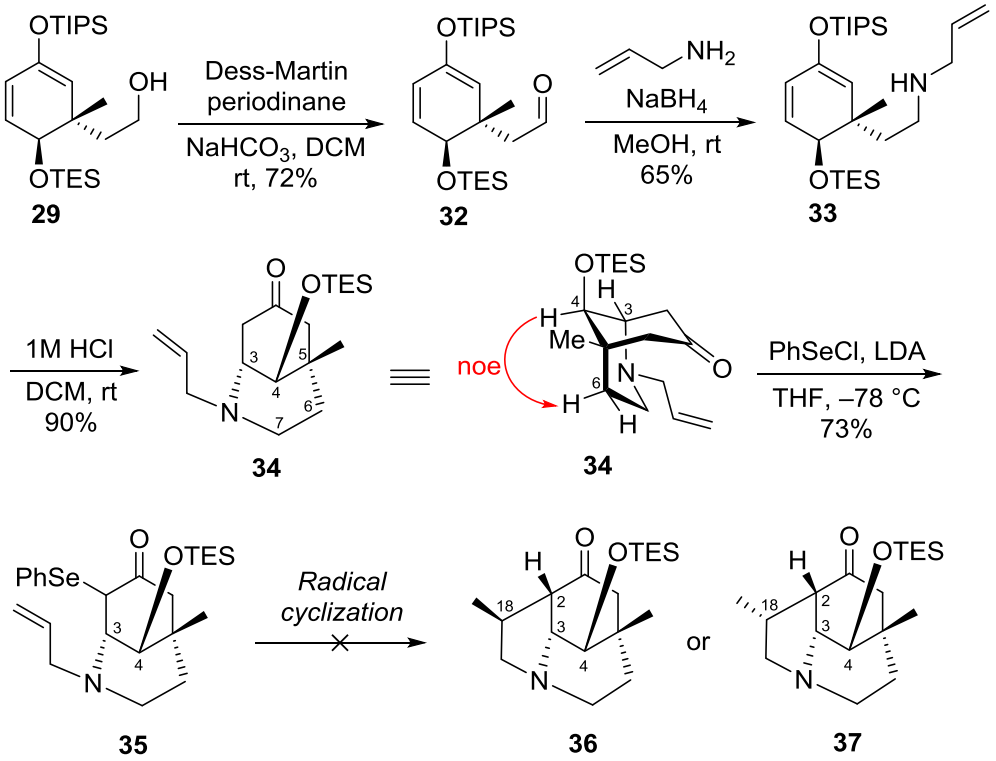
According to our synthetic plan, the enantioenriched ketone **24** was oxidized to α, β-unsaturated ketone **25** in 76% yield upon treatment with IBX[19] in DMSO (Scheme 3). Subsequent allylic bromination with NBS/AIBN[20] at 80 °C was found to be the only effective method for functionalizing the C4 position. The resulting bromide was smoothly converted into allylic alcohol **26** using $CaCO_3$/NaI[21] in 67% overall yield as an inseparable mixture of two diastereoisomers in a 2:1 ratio. Protection of the secondary alcohol in **26** occurred smoothly by treating **26** with TESCl/imidazole/DMAP to generate **27**. At this stage, we envisaged using a silyl enol ether as a masked C1 carbonyl group to prevent the probable *oxo*-Michael addition when the primary alcohol was liberated in the subsequent operations. Thus, enone **27** was subjected to silyl enol ether formation employing TIPSCl/NaHMDS, leading to diene **28** in 88% yield. Subsequent benzoate hydrolysis with K_2CO_3 in MeOH delivered the desired alcohol **29** and 4-*epi* isomer diol **30** in 61% and 29% yield, respectively. The relative stereochemistry of C4 in **29** was established by the NOE correlation of the subsequent bicyclic product **34** (red arrow in Scheme 4). Since our attempts towards a Mitsunobu reaction of 4-*epi* isomer **30** were



Scheme 2. Preparation of the enantioenriched intermediates **22** and **24**.



Scheme 3. Preparation of alcohol intermediate **29**.



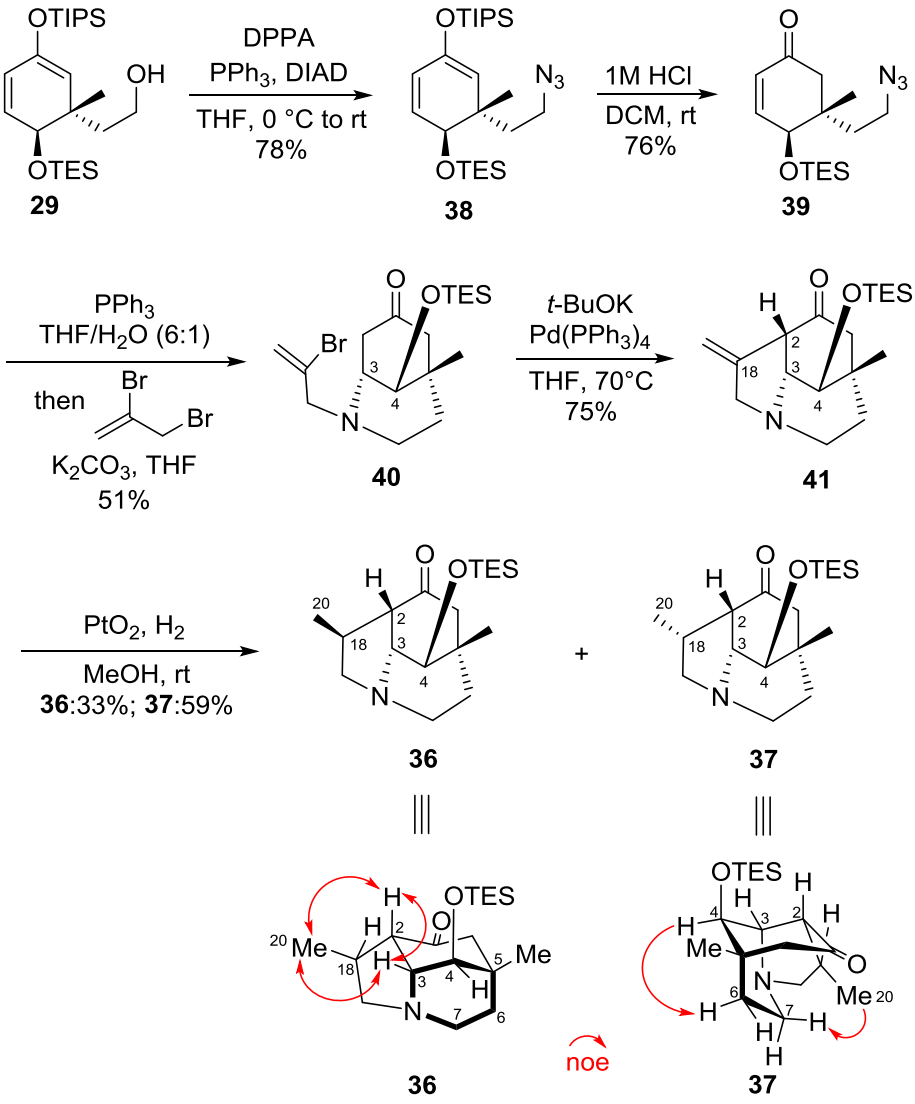
Scheme 4. Explorations into a radical cyclization strategy to achieve the ABC tricyclic core.

unsuccessful, we tried to develop an alternative strategy to inverse the configuration of secondary alcohol in **30**. As indicated in Scheme 3, we found that Dess-Martin oxidation[22] of diol **30**, followed by Luche reduction[23] afforded diol **31** in 75% overall yield as a diastereoisomeric mixture in a 2:1 ratio, then selective benzoylation of the primary alcohol and protection of the secondary alcohol provided **28** in 66% yield in 2 steps. In the event, this reaction cycle involving aforementioned four-step sequence could be conducted smoothly to improve the synthetic efficiency in the preparation of intermediate **29**.

With alcohol **29** in hand, we turned our attention to construct the ABC tricyclic core. Dess-Martin oxidation of **29** furnished aldehyde **32** (Scheme 4), which was subjected to reductive amination with allylamine/$NaBH_4$ in MeOH, delivering the substrate **33** for the next *aza*-Michael addition. Pleasingly, treating **33** with 1 M HCl in DCM readily afforded the desired cyclization product, in which **33** underwent sequential selective desilylation and *aza*-Michael addition as planned, to provide bicyclic ketone **34** with good efficiency (90% yield). Subsequent regioselective selenation of the kinetic enolate of **34** employing PhSeCl/LDA[16] afforded the desired phenyl selenide **35** in 73% yield as a single, though unassigned, diastereomer about the newly formed chiral center. We expected that the radical derived from **35** could undergo a 5-*exo*-trig cyclization onto the allylamine side-chain, concurrently setting the angular methyl group stereochemistry. Unfortunately, we failed to realize this potential radical cyclization following several attempts (including AIBN/*n*-Bu_3SnH,[16] V40/*n*-Bu_3SnH[24] and Et_3B/O_2[25]) to deliver the ABC tricyclic structure **36** or **37**.

Since the radical cyclization strategy to construct B ring was unsuccessful, inspired by the elegant works of Bonjoch[11a] and Liang,[11l] our focus turned to the Pd-catalyzed α-alkenylation protocol defined in our retrosynthetic analysis (*vide supra*). As shown in Scheme 5, alcohol **29** was converted into the desired azido derivative **38** in 78% yield with diphenylphosphoryl azide (DPPA) under Mitsunobu condition.[26] After selective desilylation with HCl, the resultant azide **39** was subjected to a one-pot three-step process involving Staudinger reaction (PPh_3, THF/H_2O) and a subsequent cascade *N*-alkylation/base-promoted *aza*-Michael addition sequence (2,3-dibromopropene, K_2CO_3) to deliver the desired azabicyclo[3.3.1]nonane framework **40** in 51% overall yield. To our delight, when bromide **40** was treated with Pd$(PPh_3)_4$ and *t*-BuOK in the heated THF for Pd-catalyzed enolate α-alkenylation,[11a,11l] it was smoothly converted to the bowl-shaped tricyclic product **41** with a newly formed C2 stereocenter in 75% yield. It was worth noting that the α-alkenylation only occurred from one face and neatly installed the C2–C18 bond in a stereoselective manner due to the intrinsic structural feature of the substrate. Finally, catalytic hydrogenation of the double bond in **41** with PtO_2 in MeOH afforded the desired product **36** in 33% yield, along with the epimer **37** in 59% yield. The relative stereochemistry of **36** and **37** was established by the NOE correlations as shown in Scheme 5 (red arrow). Other conditions such as Pd/C, $Pd(OH)_2$, Raney-Ni, Crabtree's catalyst and [Rh(cod)Cl]$_2$/PPh_3/$AgBF_4$[7] could not improve the stereochemical control, either. Thus, the ABC tricyclic framework of 21-deoxymacropodumine D (**10**) with five consecutive stereogenic centers including an all-carbon quaternary center was successfully synthesized, albeit with a disappointing 1:1.8 ratio of diastereomers. In this case, we speculated that the hydrogenation occurred dominantly from convex face of the alkene substrate, giving the unsatisfied stereoselectivity.

In summary, we have achieved the asymmetric synthesis of ABC tricyclic framework of *Daphniphyllum* alkaloid 21-deoxymacropodumine D (**10**) in 11 steps from enone **23**, which could be obtained readily in decagram scale. The key steps of our synthetic efforts include an asymmetric conjugate addition to install the C5 all-carbon quaternary center, and *aza*-Michael addition followed by Pd-catalyzed α-alkenylation to construct the desired



Scheme 5. Preparation of the ABC tricyclic frameworks **36** and **37**.

bowl-shaped tricyclic core. Further studies toward the total synthesis of 21-deoxymacropodumine D are currently underway in our laboratory.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.019.

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