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Angular hydroxymethyl directed intramolecular Diels–Alder approach for the stereo- and regioselective synthesis of pimaraditerpenes

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Abstract—The stereo- and regioselective synthetic route to pimaraditerpenes, employing an angular hydroxymethyl directed intramolecular Diels–Alder reaction of the decaline intermediate, has been developed. This synthetic approach allows prompt access to both natural pimaraditerpenes and the unnatural regioisomers, which would be potentially new anti-inflammatory pimaraditerpenes.

Recently, pimarane diterpenoids have been attracting synthetic and medicinal chemists because a variety of new biological activities as well as structural diversity of these family have continuously been reported.[1] In particular, acanthoic acid (**1**), isolated from indigenous Korean medicinal plants, *Acanthopanax Koreanum Nakai*[2] and its structural isomers such as **4** and **5** have merged as one of the important pimarane diterpenoids due to their anti-inflammatory related biological activities.[3] Both natural and unnatural regioisomers revealed an excellent suppressive activity of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α),[3e,4] which are major proinflammatory cytokines. We have also reported that the natural and synthetic pimarane diterpenoids have cyclooxygenase-2 (COX-2) and nitric oxide (NO) inhibitory activities as well as anti-inflammatory effect.[3c,g]

In addition to the interesting pharmacological profiles, this family consists of structurally unique tricyclic systems including unusual *trans*-relationship between C-8 hydrogen and C-10 methyl group as shown in Figure 1. However, few synthetic procedures for them, except

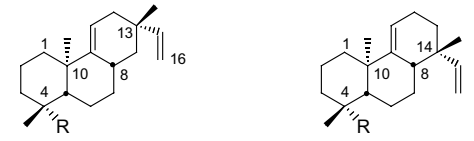

Figure 1.

securing substantial amount of pimarane diterpenoids from natural sources, limited a rapid access to the structurally diverse pimarane diterpenoids. Thus, the interesting structural features and the important biological activities of both natural and unnatural pimarane diterpenoids prompted us to initiate synthetic studies toward this family.[5]

In recent year, Theodorakis and co-workers reported the elegant total synthesis of (−)-acanthoic acid (**1**) and the structural isomer **4**[3e,6] using an intermolecular Diels–Alder reaction[7] although their synthesis suffered from moderate face selectivity (3 ~ 4:1) in Diels–Alder cycloaddition, resulting in difficulty for separation of diastereomers. We have also reported the total syntheses of isopimarol diterpene.[8] We herein report our more recent progress on the stereo- and regioselective syntheses of

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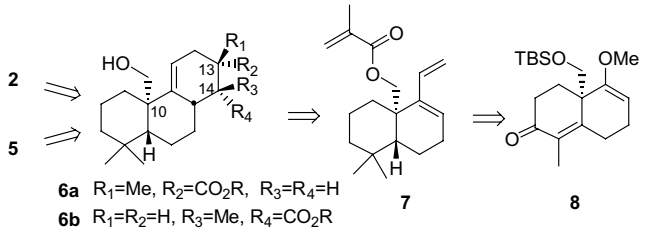


Scheme 1. Retrosynthetic analysis.

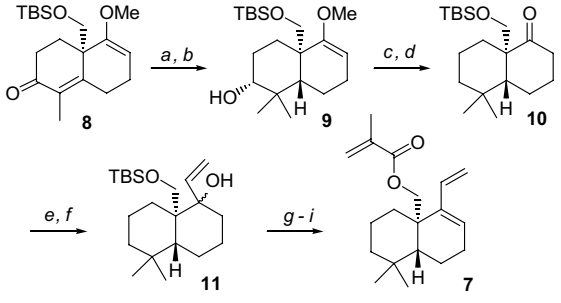
pimarane diterpenoids, which was focused on the evaluation of feasibility of our intramolecular strategy as illustrated in Scheme 1.

In contemplating the synthesis of pimaradiene **2** and its isomer **5**, it was envisioned that C-ring with the correct stereochemistries of C-8 and C-13/C-14 quaternary carbon center[9] could be constructed by the angular hydroxymethyl directed Diels–Alder cycloaddition from **7** and the subsequent hydrolysis of the resulting adduct. Such an approach would take advantage of the C-10 hydroxymethyl group to control the face selectivity of the pivotal Diels–Alder reaction, resulting in perfect stereocontrol of the quaternary carbon unit in C-ring. With regard to the intramolecular Diels–Alder reaction, we have already reported the practical synthesis of the hydroxymethylated decalones,[8c] of which angular hydroxymethyl group is stand point in our current synthetic strategy. The requisite precursor **7** would be efficiently prepared from the known bicyclic decalone **8**.[8c]

Bearing in mind the intramolecular Diels–Alder strategy, our studies toward the syntheses of pimara-9(11),15-diene (**2**) and the regioisomer **5** were commenced by preparation of the requisite Diels–Alder precursor **7** from the hydroxymethylated decalone **8**. The introduction of the methyl substituent at C-4 and the requisite stereochemistry of C-5 were executed via reductive alkylation process, as shown in Scheme 2. Treatment of the α,β-unsaturated ketone **8** with lithium in liquid ammonia followed by alkylation with MeI gave the corresponding alkylation product, which was directly subjected to $NaBH_4$ reduction to afford the alcohol **9** in an excellent yield. The decalone **10** having fully functionalized AB-ring skeleton of pimaradiene was conveniently prepared from the intermediate **9** in 94% overall yield via Barton–McCombie radical deoxygenation procedure.[10]

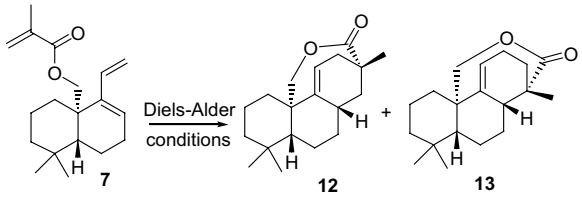
For the introduction of the diene moiety in B-ring system, the direct vinyl addition to C-9 carbonyl of the ketone **10** was initially attempted using vinyl Grignard reagent. However, the desired vinyl addition did not occur, presumably due to the steric hindrance. Thus, we adapted the smaller alkylating reagent (e.g., ethynyl Grignard reagent) in consideration of the steric environment of C-9 in the condensed structure of **10**. In the event, the bicyclic ketone **10** underwent facile Grignard addition of ethynyl magnesium bromide to afford the desired alkylation product, which was directly subjected to partial hydrogenation ($Pd/BaSO_4$, quinoline, H_2) to give the vinyl carbinol **11** in 80% overall yield. Finally, the triene **7** as an intramolecular Diels–Alder precursor was obtained from the vinyl carbinol **11** via three-step sequence (dehydration of vinyl carbinol **11** with $CuSO_4$,[11] TBS deprotection with TBAF, and esterification of the resulting alcohol with methacryloyl chloride).

With the requisite precursor **7** in hand, we intensively investigated the angular hydroxymethyl directed Diels–Alder cycloaddition. The results are summarized in Table 1. The initial intramolecular Diels–Alder reaction of the triene **7** in refluxing benzene produced a single diastereomer **13**,[12] with a quite low yield mainly due to slow reaction (entry 1). However, in addition to the efficient C-ring formation, the intramolecular cycloaddition provided a perfect stereoselectivity for two new stereogenic centers, compared to the moderate selectivity of intermolecular version.[6] Obviously, the perfect stereocontrol arises from *endo*-occupation of the tether[7] as well as α-face selectivity induced by the geometry of the tether connected angular carbon moiety, which rules out the steric interference of angular methyl in the intermolecular cycloaddition. Interestingly, the regioselectivity and the yield were quite dependent on the reaction temperature although the unnatural regioisomer was generally favored. The reaction in toluene in the sealed



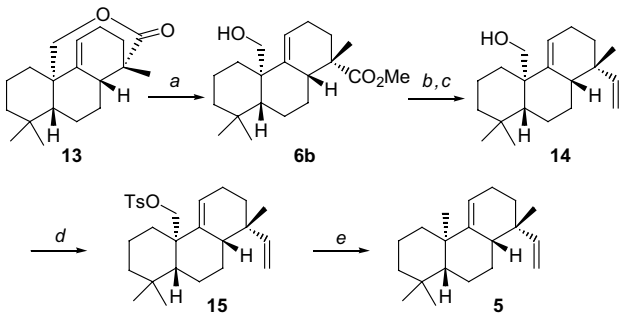
Scheme 2. Reagents and conditions: (a) Li/NH_3 (*l*), MeI, *t*-BuOH, −78 °C, 71%; (b) $NaBH_4$, EtOH, 0 °C, 99%; (c) NaH, CS_2, HMPA, imidazole, reflux, then MeI; (d) *n*-Bu_3SnH, AIBN, xylene, reflux, 94% from **9**; (e) CHCMgBr, THF, 0 °C, 81%; (f) $Pd/BaSO_4$, H_2, quinoline, MeOH, 99%; (g) $CuSO_4$, xylene, reflux, 75%; (h) TBAF, THF, 98%; (i) methacryloyl chloride, Et_3N, DMAP, THF, 0 °C, 84%.

Table 1. Intramolecular Diels–Alder reaction of the triene **7**



Entry	Conditions	Time (h)	Yields (%)[a]	Ratio (**12**:**13**)[b]
1	Benzene, 80 °C	72	<10	0:1
2	Toluene, 110 °C	72	72	1:3.5
3	Toluene, 110 °C[c]	48	78	1:10
4	Xylene, 145 °C	24	67	1.2:1

[a] Isolated yields after column chromatography.
[b] Measured by 400 MHz ^1H NMR.
[c] Sealed tube was used.



Scheme 3. Reagents and conditions: (a) NaOMe, MeOH, 95%; (b) DIBAL, toluene, −78 °C; (c) $PPh_3{}^+CH_3Br^-$, NaH, THF, 81% from **13**; (d) TsCl, pyridine, 100%; (e) NaI, Zn, HMPA, 110 °C, 70%.

tube gave the optimum result (entry 3). Considering that the type 2 intramolecular Diels–Alder reaction for the tethers containing three to five atoms produces the *meta*-regioisomer[7b] such as **13**, it is noticeable that the cycloaddition of **7** in xylene provided the reversed regioselectivity (entry 4) favoring the *para*-regioisomer, although the selectivity was not significant. Moreover, the intermolecular cycloaddition of the diene **7** is known to produce only *meta*-regioisomer.[6] Employing Lewis acid such as Me_2AlCl was not helpful for the improvement of yield and regioselectivity. The general preference of the unnatural regioisomer **13** is likely due to the favorable orientation of the dienophile for **13** in the type 2 intramolecular Diels–Alder reaction.[7b,13]

The regioselectivity for the natural pimaraditerpene **2** is expected being improved by a tether elongation as reported in the precedents.[7b] However, at this stage, we were inspired by the recent report that the methyl ester of the unnatural pimaraditepene **4**, inhibits up to 99% of TNF-α production at noncytotoxic concentration[3e] coupled with the perfect stereo- and regioselectivity of the intramolecular cycloaddition for **5**, which is not synthetically accessible from the natural product. Thus, we decided to pursue the completion of total synthesis of the isopimaradiene **5** in view of the medicinal chemistry standpoint as shown in Scheme 3.

The lactone **13** was opened with NaOMe to produce the hydroxy ester **6b**, which was transformed into the corresponding olefin **14** by DIBAL reduction and subsequent Wittig olefination in 81% overall yield. Finally, tosylation of the primary alcohol **14**, followed by reductive cleavage of the resulting tosylate **15** using NaI and Zn, provided the isopimaradiene **5** in 70% yield.[14]

In summary, we have developed an intramolecular Diels–Alder route for the stereo- and regioselective synthesis of pimaraditerpenes of structural diversity. As far as we understand, it is the first example for the type 2 intramolecular Diels–Alder reaction of the bicyclic system, in which the dienophile is directly tethered. Although the regioselectivity for the natural pimaradiene was not high as we anticipated, the excellent stereocontrol of the C-8 and C-13/C-14 stereogenic centers as well as the selective construction of pimaraditerpene skeletons for both natural and unnatural regioisomers attests to the significant synthetic utility of the angular hydroxymethyl directed cycloaddition approach in terms of the rapid access to a variety of pimaraditerpenes. Considering necessity of incorporation and removal of the regiocontrolling group (e.g., –SPh) in the diene for the intermolecular cycloaddition, this approach seems to be advantageous in synthetic efficiency in spite of low regioselectivity for natural pimaraditerpenes. As a synthetic application, the synthesis of the isopimaradiene **5** has also been accomplished in 19% overall yield through 13 linear steps from the known decalone **8**. At present, improvement of the regioselectivity of the key intramolecular Diels–Alder reaction and development of novel anti-inflammatory pimaraditerpenes by employing this approach are in good progress and the successful results will be published in due courses.

Acknowledgements

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12. The structure of the cycloadduct **13** was confirmed by an extensive NMR studies including COSY, NOESY, HMBC, and HMQC. ^{1}H NMR (400 MHz, $CDCl_3$) of the isomer **12**: δ 5.68–5.62 (m, 1H), 4.56 (d, 1H, $J = 11.2$ Hz), 3.52 (d, 1H, $J = 11.2$ Hz), 2.20–1.16 (m, 16H), 1.15 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) of the isomer **13**: δ 5.61–5.55 (m, 1H), 4.71 (d, 1H, $J = 11.2$ Hz), 3.60 (d, 1H, $J = 11.2$ Hz), 2.14–1.16 (m, 16H), 1.19 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H).
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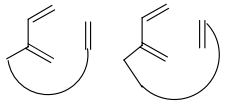
Type 2 intramolecular Diels–Alder reaction



14. Spectral data of isopimaradiene **5**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.91 (dd, 1H, $J = 11.2, 16.8$ Hz), 5.45 (m, 1H), 5.06–4.92 (m, 2H), 2.28–1.08 (m, 16H), 1.03 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.90 (m, 3H). IR ($CHCl_3$): 2960, 1460, 1375, 998, 910 cm^{-1}. LRMS (EI) *m/z*: 272 (M^+). HRMS (EI) calcd for $C_{20}H_{32}$ (M^+) 272.2504, found 272.2495.