Natural Products

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# Construction of Two Vicinal Quaternary Carbons by Asymmetric Allylic Alkylation: Total Synthesis of Hyperolactone C and (−)-Biyouyanagin A**

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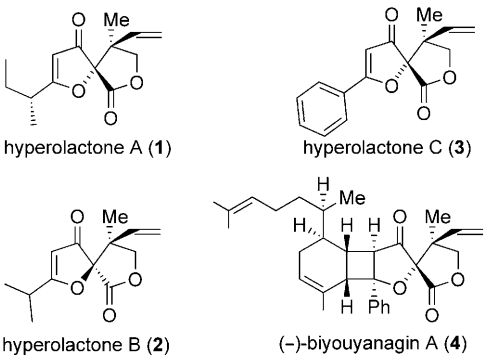
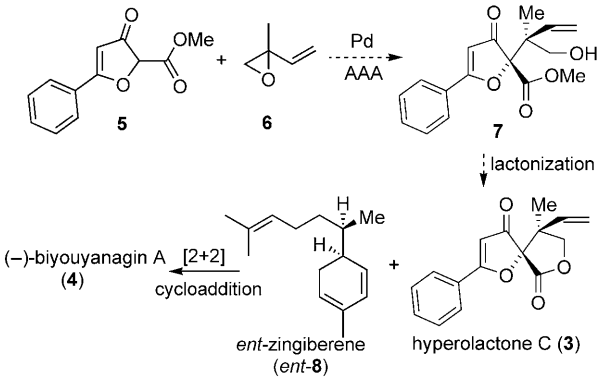
*Dedicated to Professor Zhen Yang on the occasion of his 50th birthday*

The motif of two vicinal quaternary carbon centers is found in a wide range of bioactive natural products such as hyperolactones A–C[1] and (−)-biyouyanagin A[2] (Scheme 1). The interesting biological activities and unique structures of these compounds have stimulated many total syntheses.[3] In general, the stereoselective construction of two vicinal quaternary carbon centers relys on substrate control. Only a few catalytic asymmetric C–C bond-forming reactions have been useful for constructing all-carbon quaternary stereocenters.[4] The catalytic asymmetric synthesis of two vicinal quaternary carbon centers with high diastereoselectivity and enantioselectivity remains a formidable challenge.




***Scheme 1.*** Natural products with two vicinal quaternary carbon centers.

Palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reactions, which were pioneered by Trost et al., have proven to be a powerful method for the preparation of a wide variety of chiral building blocks with high diatereo- and enantioselectivity.[5] Trost et al. have also demonstrated the application of Pd-AAA reactions in the construction of single quaternary carbon centers.[6] However, to the best of our knowledge, there is no precedent for using Pd-AAA reactions to install two vicinal quaternary carbon centers. In our synthetic studies toward hyperolactone C (**3**) and (−)-biyouyanagin A (**4**), we have devised a novel synthetic strategy which features the use of Pd-AAA to construct the key vicinal quaternary carbon stereocenters. As shown in Scheme 2, we envisioned that if nucleophilic β-ketoester **5** and electrophilic allylic donor isoprene monoepoxide **6** could be coupled by a Pd-AAA reaction, then a short and efficient synthesis of hyperolactone C (**3**) could be realized after lactonization of the Pd-AAA product **7**. Subsequently, a photoinduced [2+2] cycloaddition reaction between hyperolactone C (**3**) and **8** would give (−)-biyouyanagin A (**4**). This strategy would not only provide a powerful method to construct two vicinal quaternary carbon centers in a highly stereoselective manner, but would also help gain entry to a range of hyperolactone C and biyouyanagin A analogues through diverted total synthesis.[7] Herein, we report our successful construction of two vicinal quaternary carbon centers by a Pd-AAA reaction. By using this strategy, concise and efficient total syntheses of hyperolactone C (**3**) and (−)-biyouyanagin A (**4**) have been achieved. The unnatural enantiomer, *ent*-hyperolactone C and (+)-biyouyanagin A, have also been prepared simply by switching the chiral ligand




***Scheme 2.*** Proposed construction of two vicinal quaternary carbon centers and the synthetic plan for hyperolactone C and (−)-biyouyanagin A.

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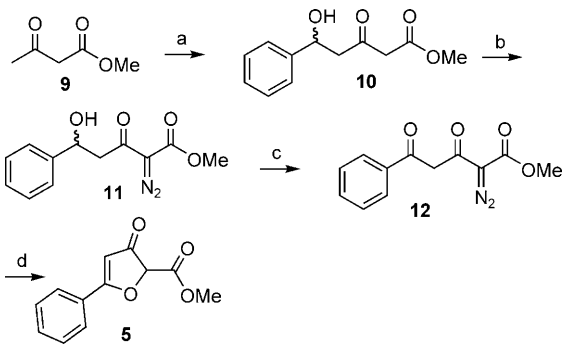
in the Pd-AAA reaction and changing the coupling partner in the photoinduced [2+2] cycloaddition reaction.

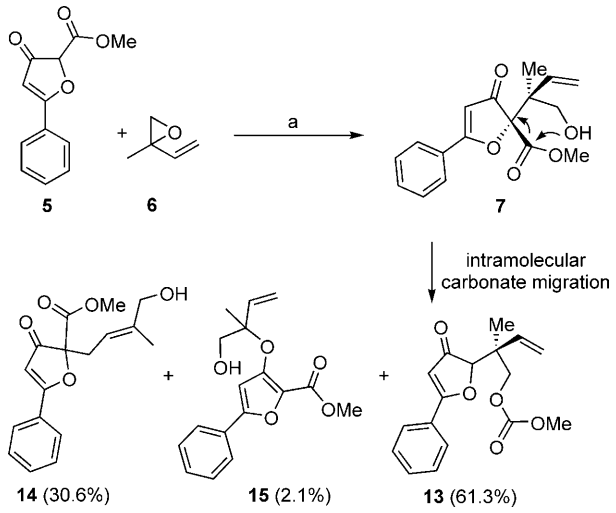
As shown in Scheme 3, the synthesis of the Pd-AAA precursor β-ketoester **5** commenced with benzaldehyde and methyl acetoacetate, which were converted into δ-hydroxy-β-oxo-pentanoate **10** by using the dianion method developed by Huchin and Weiler.[8] After treatment of **10** with $TsN_3$ in



***Scheme 3.*** Synthesis of β-ketoester **5**. Reagents and conditions: a) NaH, THF, 0°C, 0.5 h; then *n*BuLi, THF, 0.5 h; benzaldehyde, THF, 2 h, 92%; b) $TsN_3$, $Et_3N$, MeCN, 2 h, 88%; c) DMP, $CH_2Cl_2$, 2 h, RT, 91%; d) $[Rh_2(OAc)_4]$, $CH_2Cl_2$, RT, 54%. DMP = Dess–Martin periodinane, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.

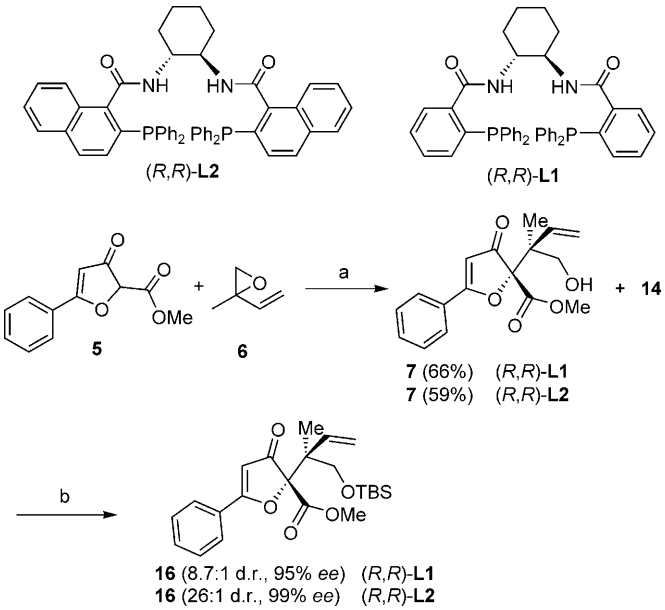
$CH_3CN$, the corresponding α-diazo-β-ketoester **11** was obtained in 88% yield.[9] Exposure of **11** to Dess–Martin periodinane in $CH_2Cl_2$ at room temperature led to the formation of the corresponding α-diazo-β-ketoesters **12**.[10] Then **12** was smoothly transformed into β-ketoester **5** in the presence of a catalytic amount of $[Rh_2(OAc)_4]$ in $CH_2Cl_2$ through a hydrogen migration process.[11]

With **5** in hand, the key Pd-AAA reaction was investigated. As shown in Scheme 4, β-ketoester **5** was treated with ligand (*R*,*R*)-**L1** (3 mol%) and $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%) in the presence of isoprene monoepoxide **6**.[12] Upon quenching the reaction after 30 minutes at room temperature, none of the desired product **7** was isolated. After careful analysis of the $^1H$ and $^{13}C$ NMR spectra of all the compounds that were isolated, we found that the major product was **13** (61.3% yield) as well as **14** (30.6% yield) and **15** (2.1% yield). The formation of **13** suggested that the expected Pd-AAA reaction for the construction of the two vicinal quaternary carbon centers did take place, but that the branched product **7** underwent further intramolecular carbonate migration (see **7**→**13**) via a five-membered-ring intermediate to form **13** as a result of the prolonged reaction time.



***Scheme 4.*** Attempted Pd-AAA of ketone **5**. Reagents and conditions: a) (*R*,*R*)-**L1** (3 mol%; see Scheme 5 for structure), $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%), $CH_2Cl_2$, RT, 30 min. dba = *trans*,*trans*-dibenzylideneacetone.

The above hypothesis turned out to be correct: when the reaction was quenched within ten minutes, the desired branched product **7** and its linear isomer **14** were obtained in 66% and 31% yield, respectively (Scheme 5). Product **7** was unstable at room temperature and it slowly underwent



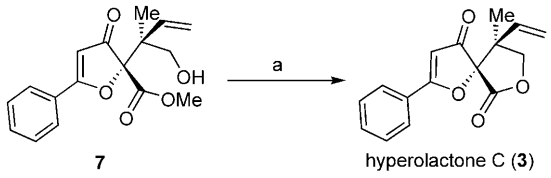
***Scheme 5.*** Construction of two vicinal quaternary carbon centers by Pd-AAA. Reagents and conditions: a) (*R*,*R*)-**L1** or (*R*,*R*)-**L2** (3 mol%), $[Pd_2(dba)_3]\cdot CHCl_3$ (1 mol%), $CH_2Cl_2$, RT, 10 min; b) TBSCl, imid, DMF, RT, 75%. DMF = *N*,*N*-dimethylformamide, imid = imidazole, TBS = *tert*-butyldimethylsilyl.

lactonization to form hyperolactone C (**3**). After separation of the isomers, the primary alcohol of **7** was protected as its TBS ether **16**. It was found that the Pd-AAA reaction took place with high diastereoselectivity (8.7:1) and excellent enantioselectivity (95% *ee*), even though a low branched to linear regioisomeric ratio was obtained (**7**/**14** = 2.1:1). To improve the selectivity of the reaction, ligand (*R*,*R*)-**L2** was used. This time the desired product **7** was obtained with higher diastereoselectivity (26:1) and better enantioselectivity (99% *ee*), but in slightly lower yields for both **7** (59%) and **14** (26%). When ligand (*R*,*R*)-**L2** was switched to (*S*,*S*)-**L2**, *ent*-**7** could be synthesized (Table 1, entry 2).

With these optimized reaction conditions, we sought to probe the scope of the Pd-AAA reaction with respect to the

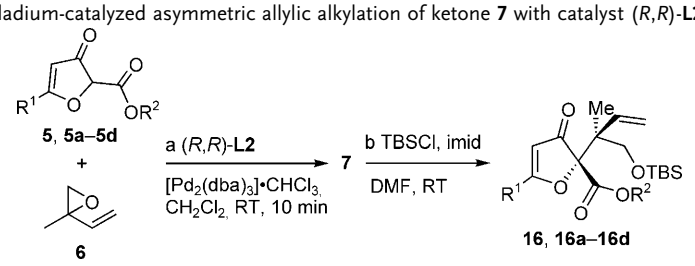
  

nature of the β-ketoester component. Therefore, β-ketoesters **5a**–**5d** were prepared by a similar protocol to that described in Scheme 3. As summarized in Table 1, **5a**–**5d** reacted smoothly with isoprene monoepoxide **6** under the reaction condition developed with (*R*,*R*)-**L2** as the chiral ligand. Substrates with various substitution patterns gave the expected products in moderate yield, with high diastereoselectivity, and excellent enantioselectivity (99% *ee*). Both electron-rich (entry 3) and electron-poor (entry 4) functionalities on the aromatic ring could be accommodated. Isopropyl and benzyloxyethyl substitutents (entries 5 and 6) also gave similar results.




***Scheme 6.*** Synthesis of hyperolactone C. Reagents and conditions: a) PTSA (20 mol%), $CH_2Cl_2$, RT, 1 h, 85%. PTSA = toluene-*p*-sulfonic acid.

***Table 1:*** Palladium-catalyzed asymmetric allylic alkylation of ketone **7** with catalyst (*R*,*R*)-**L2**.



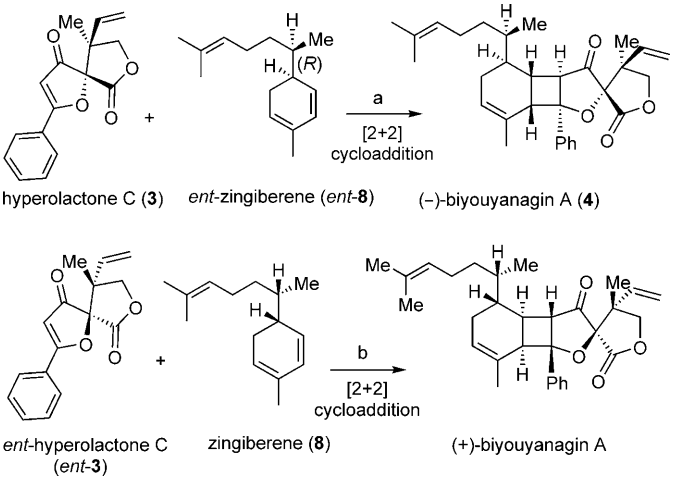

| Entry | Substrate | d.r. (**7**/**14**)[a] | Product[b] | Yield [%][c] | *ee* [%][a] |
|---|---|---|---|---|---|
| 1 | **5** ($R^1$ = Ph, $R^2$ = Me) | 26:1 (2.1:1) | **16** | 59 | 99 |
| 2[d] | **5** | 23:1 (*ent*-**7**/**14**=2.3:1) | *ent*-**16** | 54 | 99 |
| 3 | **5a** ($R^1$ = *p*-OMeC$_6$H$_4$, $R^2$ = Et) | 32:1 (1.8:1) | **16a** | 57 | 99 |
| 4 | **5b** ($R^1$ = *p*-ClC$_6$H$_4$, $R^2$ = Et) | 53:1 (1.6:1) | **16b** | 68 | 99 |
| 5 | **5c** ($R^1$ = isopropyl, $R^2$ = Me) | 8.3:1 (2.8:1) | **16c** | 55 | 99 |
| 6 | **5d** ($R^1$ = $(CH_2)_2$OBn, $R^2$ = Me | 56:1 (2.2:1) | **16d** | 48 | 99 |

[a] **7**/**14** = regioisomeric ratio of branched to linear compounds. [b] Determined from analysis of the TBS ether **16** by HPLC on a chiral stationary phase. [c] Yield of isolated product **7** after column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 2:1). [d] (*S*,*S*)-**L2** was used. Bn = benzyl.

Having developed an efficient Pd-AAA protocol to construct the two vicinal quaternary carbon centers in hyperolactone C (**3**) and (-)-biyouyanagin A (**4**), we then proceeded to finish the total synthesis of hyperolactone C. As we mentioned before, intermediate **7** slowly underwent lactonization to generate hyperolactone C (**3**). This process was significantly accelerated by treatment with a catalytic amount of PTSA in $CH_2Cl_2$ at room temperature, and hyperolactone C (**3**) was generated with d.r. 26:1 in 85% yield after 1 hour (Scheme 6). Kraus and Wei[3d] reported that the diastereomer of **7**, which was isolated as the by-product in their elegant synthesis of racemic hyperolactone C, could not be converted into a lactone using heat, acid (PTSA), or base (*t*BuOK, NaH, or KH) catalysis. After careful analysis and comparison of the NMR data for both the by-product reported by Kraus and Wei and **13** obtained by us, we discovered that the so-called diastereomer of **7** was actually **13** (see the Supporting Information). The spectroscopic data of our synthetic hyperolactone C (**3**; $^1$H, $^{13}$C NMR, IR, and HRMS) are consistent with those of the natural product.[1] *Ent*-hyperolactone C was also prepared by us using the same method.

To synthesize (−)-biyouyanagin A (**4**), *ent*-zingiberene (*ent*-**8**)[13] was prepared according to the procedure reported by Nicolaou et al.[3f,g] The preparation of **4** was achieved by employing the reported biomimetic photoinduced [2+2] cycloaddition (Scheme 7).[3f,g,14] All the spectroscopic data of synthetic (−)-biyouyanagin A (**4**; $^1$H, $^{13}$C NMR, IR, and HRMS) are consistent with those of the natural product.[2] (+)-Biyouyanagin A, which is the unnatural enantiomer of (−)-biyouyanagin A (**4**), could also been synthesized through the [2+2] cycloaddition of *ent*-hyperolactone C (*ent*-**3**) and zingiberene (**8**; Scheme 7). Compound **8** was isolated from the powder *Zingiber officinale Roscoe*.[15] Notably, irradiation of a mixture of zingiberene (**8**) and hyperolactone C (**3**) under the same reaction condition led to a complex mixture.

In summary, we have developed a successful strategy for the construction of two vicinal quaternary carbon centers with




***Scheme 7.*** Total synthesis of natural (−)-biyouyanagin A (**4**) and its enantiomer (+)-biyouyanagin A. Reagents and conditions: a) *hν*, **3**, (1.0 equiv), *ent*-**8** (4.0 equiv), 2′-acetonaphthone (1.0 equiv), $CH_2Cl_2$, 5 °C, 8 h, 39%, b) *hν*, *ent*-**3**, (1.0 equiv), *ent*-**8** (6.0 equiv), 2′-acetonaphthone (1.0 equiv), $CH_2Cl_2$, 5 °C, 8 h, 43%.

high diatereoselectivity (up to 56:1) and excellent enantioselectivity (99% *ee*) by using a palladium-catalyzed asymmetric allylic alkylation reaction. This strategy has enabled the concise and efficient total syntheses of natural hyperolactone C and (−)-biyouyanagin A from benzaldehyde in only six and seven steps, respectively. The corresponding overall yields were 20% and 8%. The unnatural enantiomer *ent*-hyperolactone C and (+)-biyouyanagin A were also prepared by simply switching the chiral ligand in the Pd-AAA reaction and by changing the coupling partner in the final photoinduced [2+2] cycloaddition reaction.

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