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# Efficient construction of a chiral all-carbon quaternary center by asymmetric 1,4-addition and its application to total synthesis of (+)-bakuchiol

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ABSTRACT

The conjugate addition of lithium divinylcuprate to (4*S*,2′*E*)-3-(6′-TBDPS-3′-methylhex-2′-enoyl)-4-phenyloxazolidin-2-one proceeded efficiently to create a chiral all-carbon quaternary center with a high diastereoselectivity (*R*:*S* = 95:5). The absolute configuration of the newly generated chiral center was confirmed by applying this methodology to the total synthesis of (+)-bakuchiol.



Over the past decade, we have reported a number of unique vibsane-type diterpenes and have studied them chemically and biologically.[1] Vibsane-type diterpenes, which are classified as 7-membered, 11-membered, and rearranged types according to their core ring structures, share the common C-11 chiral all-carbon quaternary center in these molecules (Fig. 1). In the course of our project aimed at asymmetric synthesis[2] of vibsane-type diterpenes, one of the most critical issue is most likely to be the development of synthetic methods for the construction of the C-11 chiral all-carbon quaternary center. Efficiently generating the chiral quaternary carbon centers[3] that widely exist in the core structure of various natural products has become a vital subject in the field of natural products synthesis. Recently, Alexakis[4] reported a versatile approach to the construction of the all-carbon quaternary stereocenters by the copper-catalyzed asymmetric conjugate addition of saturated alkyl or aryl Grignard reagents to trisubstituted cyclohexenones using chiral $C_2$-symmetric imidazolidinium ligands. On the other hand, although numerous diastereoselective 1,4-additions of α,β-unsaturated carboxylic acid derivatives bearing chiral auxiliary[5,6] have been reported, this kind of approach has remained unexplored for creating chiral quaternary stereocenters. Herein, we report efficient construction of the chiral all-carbon quaternary center with a vinyl moiety that would permit post-functional group manipulation by the conjugate addition of lithium divinylcuprate to chiral 3-(β-alkyl-β-methyl-α-enolyl)-4*S*-phenyloxazolidin-2-one, and demonstrate that this method provides a versatile chiral quaternary carbon source for the synthesis of natural products by its use to the total synthesis of (+)-bakuchiol.

First, (4*S*,2′*E*)-3-(6′-TBDPS-3′-methylhex-2′-enoyl)-4-phenyloxazolidin-2-one (**3**), a chiral acceptor suitable for asymmetric 1,4-addition, was prepared from 4-pentyn-1-ol (**1**) in 3 steps as shown in scheme 1. Specifically, **1** was converted to the corresponding iodoalkene by employing the Negishi protocol,[7] and then a hydroxy group was protected as a TBDPS ether to give the 5-iodo-4-methylpentenol derivative **2** in 98% yield over 2 steps. The reaction of **2** with *N*-lithiated chiral oxazolidinone reagent, which was generated in situ by the treatment of (*S*)-(+)-4-phenyl-2-oxazolidinone with *n*-butyllithium, was performed in the presence of 10 mol % $Pd(PPh_3)_4$ under CO atmosphere (0.4 MPa) in THF at room temperature giving rise to **3** in 78% yield.[8]

With the chiral Michael acceptor **3** in hand, our efforts focused on diastereoselective additions to **3** to create the quaternary carbon center by examining several vinylcopper(I) reagents, because an introduced vinyl group is convenient for subsequent transformations to appropriate functional groups. First $(vinyl)_2CuMgBr$ species generated from vinylmagnesium bromide (10 equiv) and CuI (1 equiv) were investigated. The reaction of **3** with $(vinyl)_2CuMgBr$ in THF at −78 °C gave the desired 1,4-adduct **4** in moderate yield (Table 1, entry 1). In this case, no formation of the other diastereoisomer **5** was observed in the $^1H$ NMR spectrum of the crude mixture, but an unexpected vinyl

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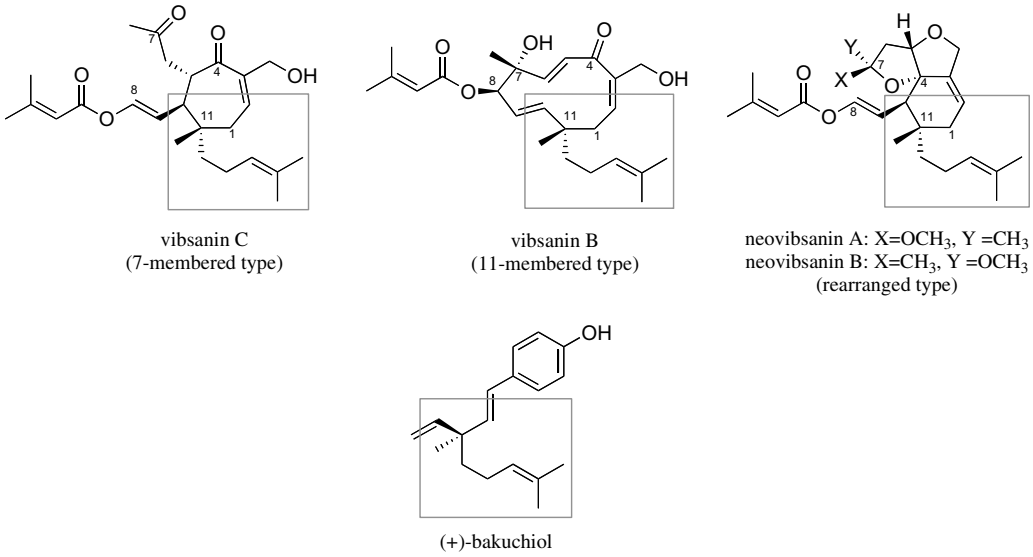
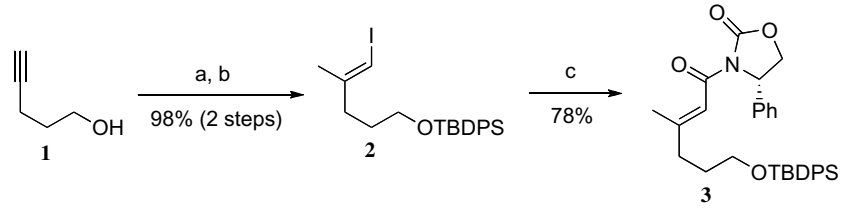
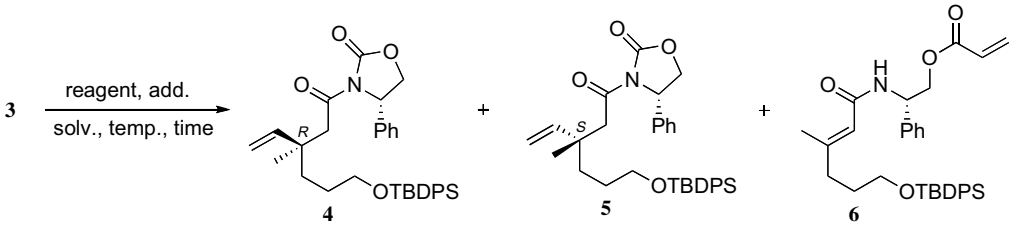



**Figure 1.** Structures of vibsane-type diterpenes and (+)-bakuchiol.




**Scheme 1.** Preparation of **3**. Reagents and conditions: (a) $Me_3Al$, $Cp_2ZrCl_2$, 1,2-dichloroethane, then $I_2$, THF; (b) TBDPSCl, $Et_3N$, DMAP, $CH_2Cl_2$; (c) (*S*)-(+)-4-phenyl-2-oxazolidinone, *n*-BuLi, THF, then **2**, 10 mol % $Pd(PPh_3)_4$, CO (0.4 MPa).

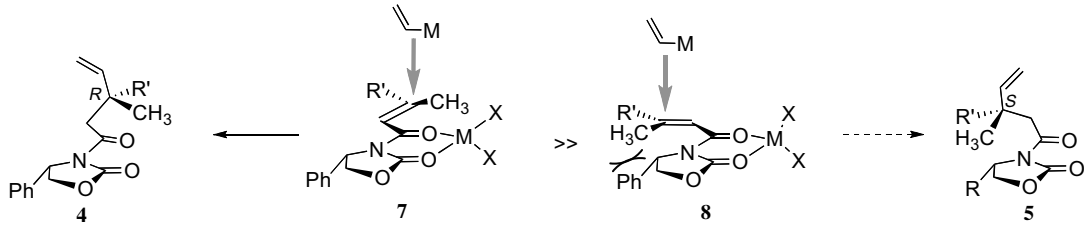
**Table 1**
Asymmetric 1,4-addition of the trisubstituted α,β-unsaturated carboxylic acid derivative **3**



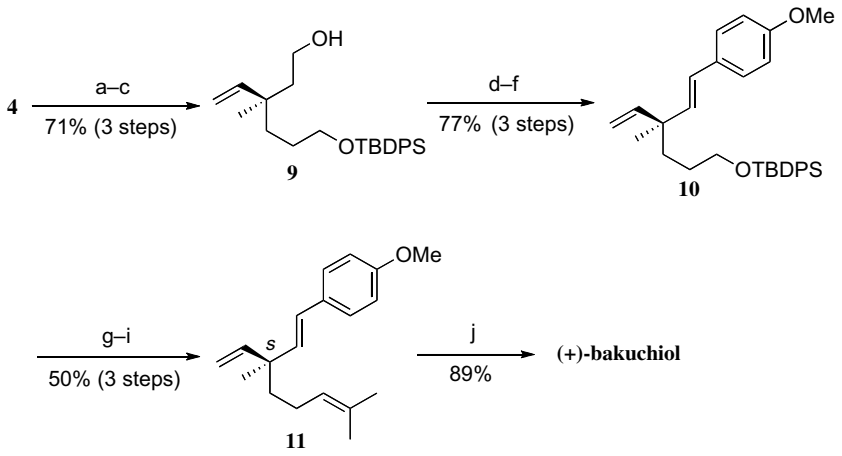

| Entry | Reagent (equiv) | Add. (equiv) | Solv. | Temp. (°C) | Time (h) | Yield of **4** (%) | (**3**:**4**:**5**:**6**)[a] |
|---|---|---|---|---|---|---|---|
| 1 | $H_2C{=}C(H)MgBr$ (10) | CuI (1) | THF | −78 | 12 | 47 | (0:43:0:57) |
| 2 | $H_2C{=}C(H)MgBr$ (5) | CuI (1) | THF | −78 | 12 | 26 | (65:26:0:9) |
| 3 | $H_2C{=}C(H)MgBr$ (2.5) | CuI (1) | THF | −78 | 12 | —[b] | (73:18:0:8) |
| 4 | *n*-BuLi (3.9)/$(vinyl)_4Sn$ (0.9) | CuCN (2) | THF | −78 | 14 | —[b] | (76:24:0:0) |
| 5 | PhLi (6.7)/$(vinyl)_4Sn$ (1.9) | CuCN (4) | $Et_2O$ | −78 to −50 | 19 | 79 | (0:95:5:0) |

[a] The ratio was determined by $^1H$ NMR (400 MHz) of the crude mixture.
[b] The reaction mixture was not purified.

adduct **6** was obtained in 57% yield. While we suspected that the generation of **6** might arise from the excess vinylmagnesium bromide, we decreased the amount of vinylmagnesium bromide to 2.5 or 5 equiv (entries 2 and 3). However, these reaction conditions could not suppress the formation of **6,** but considerably decreased the reaction rate.[9] Subsequently, we examined the 1,4-addition of **3** by using $(vinyl)_2CuCNLi_2$ that was generated from tetravinyltin with *n*-BuLi and CuCN, resulting in the sole formation of the desired 1,4-adduct with a high diastereoselectivity in spite of poor conversion rate (entry 4). We suspected that the low reactivity of the $(vinyl)_2CuCNLi_2$ was due to coexisting tetrabutyltin. Thus tetraalkyltin free vinyllithium that was prepared from tetravinyltin with PhLi was treated with CuCN to yield the $(vinyl)_2CuCNLi_2$, which was subjected to the 1,4-addition reaction with **3**. The reaction proceeded smoothly and furnished a diastereomeric mixture of the vinyl adducts **4** and **5** (95:5) in 79% yield.[10] The absolute configuration of the newly created all-carbon quaternary center for **4** and **5** was tentatively



**Scheme 2.** Proposed mechanism for the facial selectivity of asymmetric 1,4-addition.

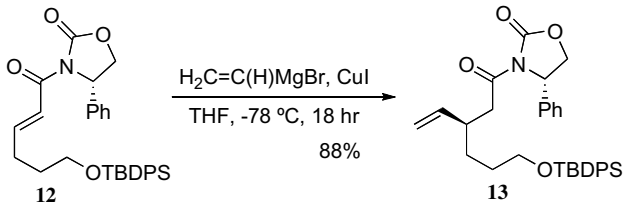


**Scheme 3.** Total synthesis of (+)-bakuchiol. Reagents and conditions: (a) LiOH, 30% $H_2O_2$, THF–$H_2O$, 0 °C to rt; (b) EtOH, EDC·HCl, 4-DMAP, $CH_2Cl_2$; (c) $LiAlH_4$, THF, 0 °C; (d) Dess–Martin periodinate, $CH_2Cl_2$; (e) *p*-methoxyphenylmagnesium bromide, THF, 0 °C; (f) MsCl, 4-DMAP, $CH_2Cl_2$; (g) HF/pyr/MeCN (1:3:5); (h) Dess–Martin periodinate, $CH_2Cl_2$; (i) $Me_2CHP^+Ph_3{\cdot}Br^-$, *n*-BuLi, THF, 0 °C; (j) MeMgI, 175 °C.

assigned as (*R*) and (*S*), respectively, based on the following mechanistic considerations: The substrate **3** is most likely to prefer the *s*-cis conformer **7** over the *s*-trans one **8** due to the steric interaction between a β-methyl group and an oxazolidinone moiety as depicted in scheme 2. The divinylcopper(I) reagent favors an approach from *si*-face of **7**, which avoids a bulky phenyl group.

Confirmation of the absolute configuration for the quaternary stereogenic center that was tentatively assigned was unambiguously made by converting **4** with a (*R*) chirality to a chirality-defined natural product, (+)-bakuchiol,[11] which was isolated from seeds of *Psoralea corylifolia* L.

Scheme 3 shows our synthetic route to (+)-bakuchiol. The oxazolidinone moiety of the 1,4-adduct **4** was hydrolized by LiOH–$H_2O_2$, and the resultant carboxylic acid was again converted to an ethyl ester with ethanol and EDC·HCl, and then reduced with $LiAlH_4$ to furnish alcohol **9** in good yield. Dess–Martin oxidation of **9** gave an aldehyde which was reacted with *p*-methoxyphenylmagnesiumbromide followed by mesylation and elimination of the generated hydroxy group, producing only the desired (*E*)-methoxyphenyl derivative **10** in 77% yield over two steps. Deprotection of TBDPS group by treatment of **10** with HF–pyridine genarated a primary hydroxy group, which was oxidized with Dess–Martin reagent to an aldehyde, which in turn was subjected to Wittig olefination, giving rise to methylbakuchiol **11** in moderate yield. The spectroscopic data[12] of **11** were identical with methylbakuchiol[11e] derived from natural (+)-bakuchiol. The optical rotation of synthetic methylbakuchiol (**11**) with an (*S*)-configuration {$[\alpha]_D^{18}$ +28.4 (*c* 1.07, $CHCl_3$)} was consistent with that of natural methylbakuchiol {$[\alpha]_D^{29}$ +31.18 (*c* 1.45, $CHCl_3$)}.[11e] Thus, the absolute configuration of the quaternary carbon center of **4** could be unambiguously established as (*R*). Finally, demethylation of **11** with MeMgI[11b] accomplished the total synthesis of (+)-bakuchiol.[13]



**Scheme 4.** Asymmetric 1,4-addition of the disubstituted α,β-carboxylic acid derivative **12**.

In conclusion, we have developed an efficient and facile methodology for constructing chiral all-carbon quaternary center via asymmetric 1,4-addition of $(vinyl)_2CuCNLi_2$ to (4*S*,2′*E*)-3-(6′-TBDPS-3′-methylhex-2′-enoyl)-4-phenyloxazolidin-2-one (**3**). To the best of our knowledge, this is the first example of the construction of a chiral all-carbon quaternary center by asymmetric 1,4-addition of a vinyl nucleophile to a tri-substituted alkene including a chiral auxiliary (see Scheme 4). Additionally, we have achieved the total synthesis of (+)-bakuchiol from the 1,4-adduct **4** in 20% overall yield over 10 steps. As part of further application of this methodology, synthetic studies of some vibsane-type diterpenes are now in progress.

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9. When the same conditions as entry 2 in table was applied to the Michael addition of (4S,2′*E*)-3-(6′-TBDPS-3′-methylhex-2′-enoyl)-4-phenyloxazolidin-2-one (**12**) that lacked the methyl group in **3**, the reaction proceeded smoothly to furnish a sole stereoisomer **13** in 88% yield (Scheme 4). This result is consistent with the Williums's result.[6f] In the case of **3**, the presence of the β-methyl group presumably interfered with the conjugated attack of vinylcuprate, favoring the 1,2-addition of excess vinyl Grignard reagents to the oxazolidione auxiliary.
10. *Typical procedure for asymmetric 1,4-addition*: PhLi (ca. 1.9 mol/L in *n*-butyl ether, 13.4 mL, 25.5 mmol) was added to tetravinyltin (1.38 mL, 7.60 mmol) at room temperature and the mixture was stirred for 30 min. The reaction mixture was diluted with ether (10 mL) and the formed white precipitate was removed by filtration through the glass filter (3 G) under argon atmosphere, the residue was washed with ether (5 mL). The dark red filtrate was added to the suspension of CuCN (1.36 g, 15.1 mmol) in ether (8 mL) via cannula at −78 °C, and then the reaction mixture was allowed to warm to 0 °C and stirred until the solution turned to dark green suspension (ca. 2 min). The supernatant was added to the solution of **3** (2.02 g, 3.80 mmol) in ether (8 mL) via cannula at −78 °C, and then the reaction mixture was stirred for 16 h at −50 °C. The reaction mixture was diluted with 10% $NH_4OH$ (80 mL) and stirred for 30 min, and then filtered through the Celite, extracted with ether (3 × 80 mL). The combined ether layers were dried with $MgSO_4$, filtered, and concentrated to give the residue, which was purified by column chromatography ($SiO_2$, hexane–EtOAc = 10:1) to give **4** (1.69 g, 3.00 mmol, 79%, dr = 95: 5) as a slightly yellow oil. *Data for* **4**: $[\alpha]_D^{18}$ −180.7 (*c* 0.26, $CHCl_3$); IR 1710, 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, *J* = 7.6 Hz, 4H), 7.26–7.44 (m, 11H), 5.82 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.39 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.94 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.82 (dd, *J* = 1.2, 17.6 Hz, 1H), 4.61 (t, *J* = 8.8 Hz, 2H), 4.23 (dd, *J* = 3.6, 8.8 Hz, 1H), 3.57 (m, 2H), 3.17 (d, *J* = 14.8 Hz, 1H), 2.87 (d, *J* = 14.4 Hz, 1H), 1.44 (m, 2H), 1.03 (s, 12H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 153.8, 145.2, 139.2, 135.6, 134.1, 129,6, 129.1, 128.7, 127.7, 126.2, 112.5, 69.6, 64.4, 57.8, 44.1, 39.8, 36.8, 27.4, 26.9, 22.8, 19.3; HRMS *m/z* (EI) $[M-H]^+$ calcd for $C_{34}H_{40}NO_4Si$, 554.2727; found, 554.2696.
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12. *Data for methylbakuchiol* (11): $[\alpha]_D^{18}$ +28.4 (*c* 1.07, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.26 (d, *J* = 16.4 Hz, 1H), 6.06 (d, *J* = 16.4 Hz, 1H), 5.88 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.11 (quint. t, *J* = 1.6, 7.2 Hz, 1H), 5.03 (dd, *J* = 1.2, 10.8 Hz, 1H), 5.01 (dd, *J* = 1.2, 17.6 Hz), 3.80 (s, 3H), 1.95 (dt, *J* = 4.0, 7.6 Hz, 2H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.58 (d, *J* = 0.8 Hz, 3H), 1,49 (m, 2H), 1.20 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 158.8, 146.1, 135.9, 131.4, 130.8, 127.2, 126.6, 124.9, 114.0, 111.9, 55.4, 42.6, 41.4, 25.8, 23.5, 23.3, 17.7; HRMS *m/z* (EI) $[M]^+$ calcd for $C_{19}H_{26}O$, 270.1984; found, 270.1969.
13. *Data for synthetic (+)-bakuchiol*: $[\alpha]_D^{18}$ +26.0 (*c* 0.45, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 16.2 Hz, 1H), 6.05 (d, *J* = 16.2 Hz, 1H), 5.87 (dd, *J* = 10.8, 17.4 Hz, 1H), 5.10 (quint. t, *J* = 1.5, 6.9 Hz, 1H), 5.03 (dd, *J* = 1.2, 10.8 Hz, 1H), 5.00 (dd, *J* = 1.2, 17.4 Hz, 1H), 1.95 (dt, *J* = 7.5, 9.0 Hz, 2H), 1.67 (d, *J* = 0.9 Hz, 3H), 1.59 (s, 3H), 1.48 (m, 2H), 1.19 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 154.7, 146.0, 135.9, 131.4, 130.9, 127.4, 126.5, 124.9, 115.4, 112.0, 42.6, 41.4, 25.8, 23.4, 23.3, 17.7; HRMS *m/z* (EI) $[M]^+$ calcd for $C_{18}H_{24}O$, 256.1821; found, 256.1827.