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Efficient Synthesis of Anastrephin via the Allylic Substitution for Quaternary Carbon Construction

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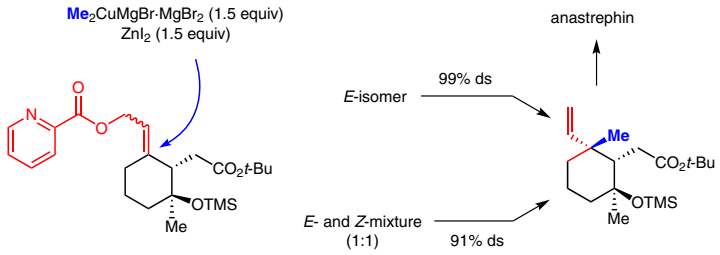

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Abstract Lactone-moiety-attached 2-cyclohexylideneethyl picolinate was prepared through the OH-directed epoxidation (98% ds) of (*R*)-3-methylcyclohex-2-en-1-ol (99% ee), Horner–Wadsworth–Emmons olefination, conversion to the allylic moiety, and epoxide ring opening with $Et_2AlCH_2CO_2t$-Bu. The allylic substitution of the picolinate with $Me_2CuMgBr{\cdot}MgBr_2$ furnished a quaternary carbon center with 92% ds. Finally, the lactonization of the product, the *tert*-butyl ester of the seco acid, under acidic conditions, afforded (–)-anastrephin.

Key words anastrephin, quaternary carbon, asymmetric synthesis, allylic substitution, copper reagent, picolinate

Anastrephin is a sex pheromone produced with epianastrephin by the Caribbean fruit fly *Anastrepha suspensa* (Loew) and the Mexican fruit fly *Anastrepha Zudens* (Loew), both of which are major fruit pests in Central America and neotropical North America[1] (Figure 1). The relative stereochemistry and absolute configuration of anastrephin were determined by degradation.[2] A quaternary chiral carbon center on the cyclohexane ring and the lactone moiety connected to the ring in a *trans* fashion are the structural features of **1**. Previously, several syntheses of **1** were reported in optically active[3] and racemic forms.[2,4] However, the former syntheses suffered from long reaction sequences and low diastereoselectivity in crucial steps for the construction of chiral carbon centers. These results prompted us to develop a stereoselective and short synthesis of **1**.

Recently, we developed a stereoselective construction of a quaternary carbon on a cyclohexane ring using the allylic substitution of cyclohexylidene allylic picolinate.[5] The method featured high regioselectivity, sufficient reactivity, and high stereoselectivity. The former two merits were ensured by using the picolinoxy leaving group,[6] whereas the

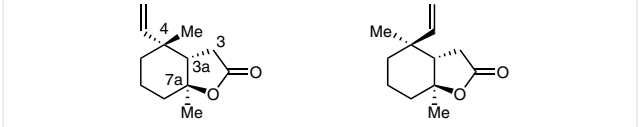
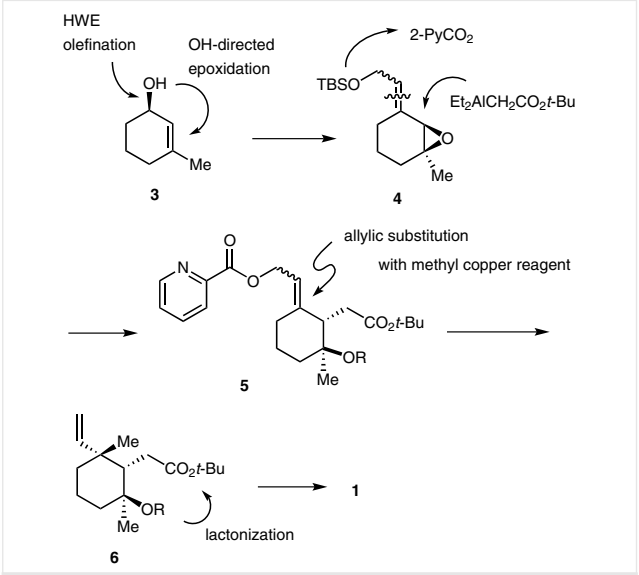


Figure 1 Structures of anastrephins

stereoselectivity stemmed from the equatorial attack of copper reagents on the stable chair conformer of the cyclohexane ring. This stereochemical control was the crucial step in the synthesis of cyclobakuchiol A[7] and axenol.[8] With this substitution in hand, in the present study, we designed the allylic substitution of **5** with a methyl copper reagent to furnish the required quaternary carbon in **6** (Scheme 1). Among the *E*- and *Z*-olefin isomers of allylic picolinate **5**, conformational instability of the *Z*-isomer by the steric interaction between vicinal side chains was apparent, whereas the effect of such steric congestion on stereoselectivity and reactivity was unprecedented. On the other hand, the *E*-isomer of **5** was expected to afford **6** diastereoselectively through a stable conformer. Regarding the installation of the lactone side chain of **5**, we applied the Battiste's epoxide ring opening of **4** with $Et_2AlCH_2CO_2t$-Bu.[9] Furthermore, conversion of allylic alcohol **3** to epoxide **4** was envisioned through OH-directed epoxidation and subsequent installation of the allylic moiety through Horner–Wadsworth–Emmons olefination. Herein, we present the results of this investigation.

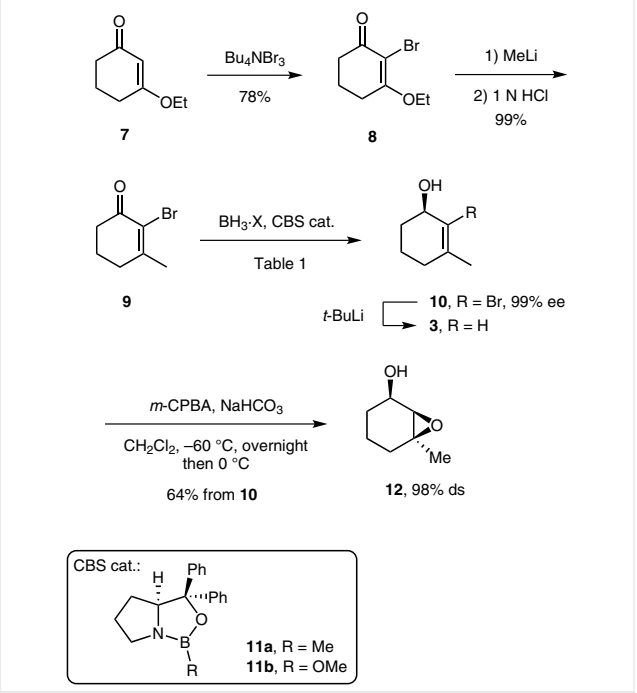
The synthesis of **3** and subsequent epoxidation is delineated in Scheme 2. First, **7** was converted into bromide **8** with Bu_4NBr_3 in 78% yield. The methylation of **8** with MeLi followed by exposure to aqueous HCl produced **9** quantitatively.[10] The CBS reduction of **9** with **11a** and BH_3·THF according to the literature procedure[11] afforded alcohol **10** in



Scheme 1 Synthetic strategy via allylic substitution

70% yield but with a comparable ee of 74% (lit.[11] 80% ee; Table 1, entry 1). We then investigated the reduction under various conditions: 87% ee was attained using BH_3·Et_2NPh and MeO catalyst **11b**[12] at 0 °C (Table 1, entry 2). The use of a lower temperature (–5 °C) effectively raised the ee to 98% and the yield was 90% (Table 1, entry 3). The ee was further increased by recrystallization from hexane to >99% with 89% recovery. In contrast, a combination of BH_3·Et_2NPh and **11a** required a relatively higher temperature (30 °C), affording 56% ee of **10**. The debromination of **10** (>99% ee) with *t*-BuLi produced alcohol **3** in good yield without racemization as analyzed by chiral HPLC (>99% ee).[13] Finally, the epoxidation of **3** with *m*-CPBA at –60 °C overnight followed by a gradual warming to 0 °C gave **12** in 64% yield over two steps with 98% ds as determined by ^1H NMR spectroscopy. On the other hand, expoxidations at –40 °C and 0 °C resulted in 96% and 90% ds, respectively. The moderate yield of **12** from **10** was mainly because of the volatile nature of **3**.

TPAP-catalyzed oxidation of **12** with NMO produced somewhat volatile epoxy ketone **13** (Scheme 3).[14] Without purification, this ketone was subjected to Horner–Wadsworth–Emmons olefination under standard conditions to afford ester **14** in 57% yield as a 47:53 mixture of *E*- and *Z*-olefins. Ester **14** was then reduced with DIBAL, and the resulting allylic alcohol **15** was converted into TBS ether **4** in good yield. Epoxide ring opening of **4** with $Et_2AlCH_2CO_2t$-Bu according to the procedure developed by Battiste[9] was successful, affording **16** in 92% yield. However, the procedure consisting of a solvent change from hexane to THF after the preparation of $LiCH_2CO_2t$-Bu from $MeCO_2t$-Bu and LDA in hexane was practically complicated. To detour the solvent exchange, the lithium enolate in hexane was diluted with THF (final hexane–THF ratio of 1:1) and subjected to a reaction with epoxide **4** at –40 °C to –15 °C for four hours to produce **16** in 91% yield. The olefin isomers of **16** were easily separated by column chromatography on silica gel to determine ^1H NMR and ^{13}C NMR spectra to be consistent with those previously reported. In a similar manner, the use of hexane–DME (1:1) afforded **16**, which was subjected to



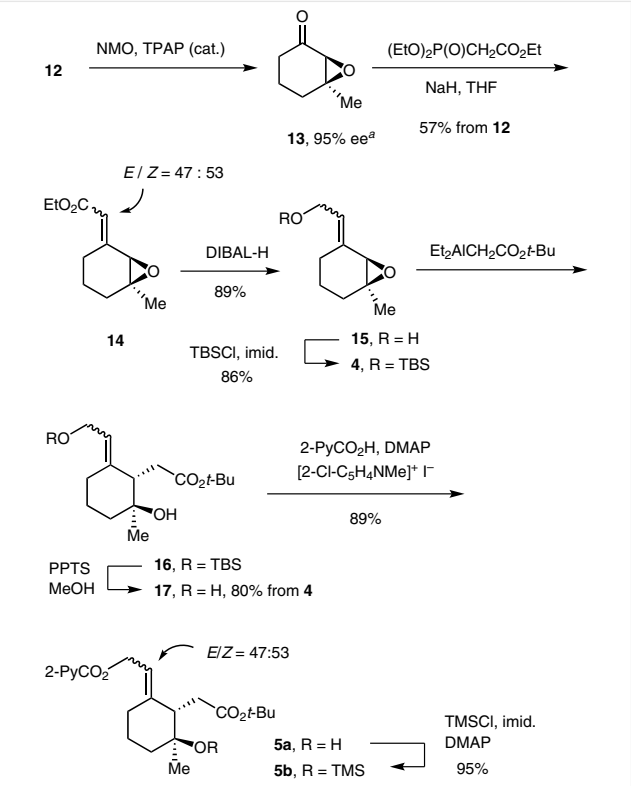
Scheme 2 Preparation of alcohol **3**

Table 1 CBS Reduction of **9**

Entry	Cat. (mol%)	BH_3·X (equiv)	Temp (°C)	Time (h)	Yield (%)	ee (%)[a]
1	**11a** (10)	BH_3·THF (1.3)	+30	18	70	74
2	**11b** (10)	BH_3·Et_2NPh (1.2)	0	21	81	87
3	**11b** (5)	BH_3·Et_2NPh (1.2)	–5	18	90 (89)[b]	98 (99.1)[b]
4	**11a** (10)	BH_3·Et_2NPh (1.3)	+30	2	65	56

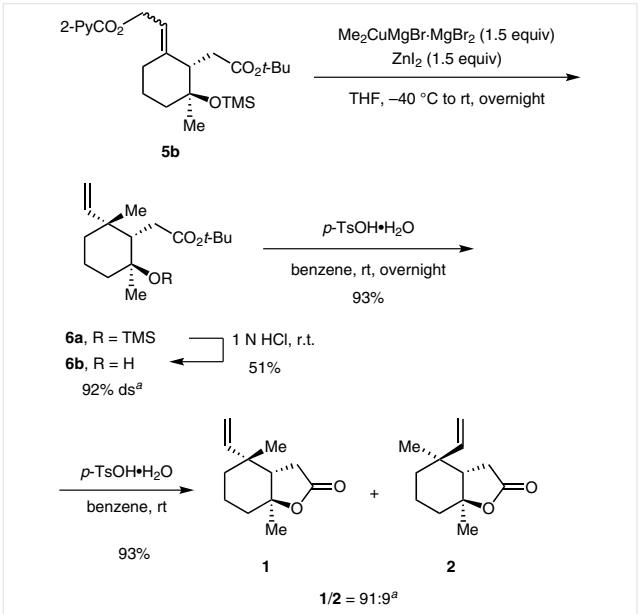
[a] Determined by chiral HPLC.
[b] Recrystallization from hexane with 89% recovery.

desilylation with PPTS (1.5 equiv) in CH_2Cl_2–MeOH (1:1) to produce diol **17** in 80% yield from epoxide **4**. The esterification of **17** with 2-$PyCO_2H$ and $[2\text{-}ClC_5H_4NMe]^+ I^-$ proceeded regioselectively at the primary hydroxyl group, affording picolinate **5a** in 89% yield. Subsequently the remaining tertiary hydroxyl group of **5a** was protected as the TMS ether to produce **5b** as a 47:53 mixture of the *E*- and *Z*-isomers in high yield. In a similar manner, the *E*- and *Z*-isomers of **5b** were individually synthesized from (*E*)- and (*Z*)-**16**, respectively.



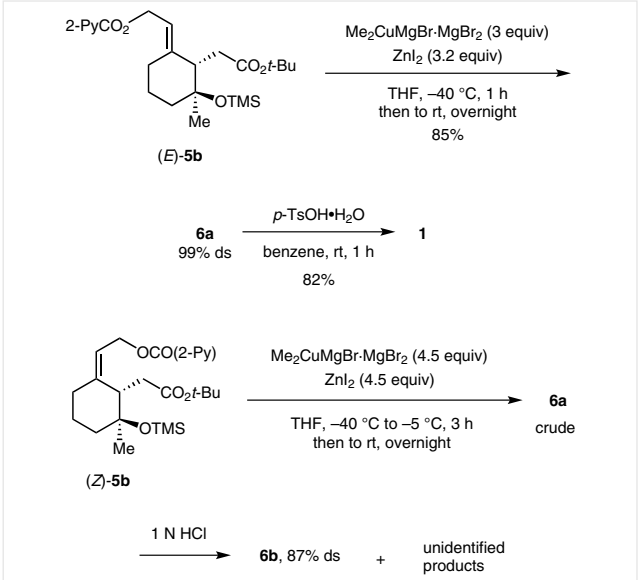
Scheme 3 Preparation of allylic picolinate **5b**. [a] Calculated based on 99% ee of **10** and 98% ds of **12**.

The allylic substitution of **5b** with methyl copper reagent $Me_2CuMgBr{\cdot}MgBr_2$ (1.5 equiv) derived from MeMgBr and $CuBr{\cdot}Me_2S$ in the presence of ZnI_2 (1.5 equiv) gave TMS ether **6a**, which was hydrolyzed to alcohol **6b** in 51% yield with 92% ds as determined by ^1H NMR spectroscopy (Scheme 4). Finally, **6b** was exposed to *p*-$TsOH{\cdot}H_2O$ to furnish anastrephin (**1**) in 93% yield. The ^1H NMR spectrum of the crude product was clean and showed no formation of byproducts such as *cis*-lactone (7a-*epi*-anastrephin) and olefin(s), which are likely products through the tertiary cation, whereas olefin(s) and polycondensation products are formed by the attempted lactonization of the methylene analogue–seco acid of **16** under acidic conditions.[15] The ^1H NMR and ^{13}C NMR spectra of **1** were consistent with those reported previously.[3a,b] The structure was also supported by the ^{13}C–APT spectrum (APT: attached proton test).



Scheme 4 Last stage of the synthesis. [a] Determined by ^1H NMR spectroscopy.

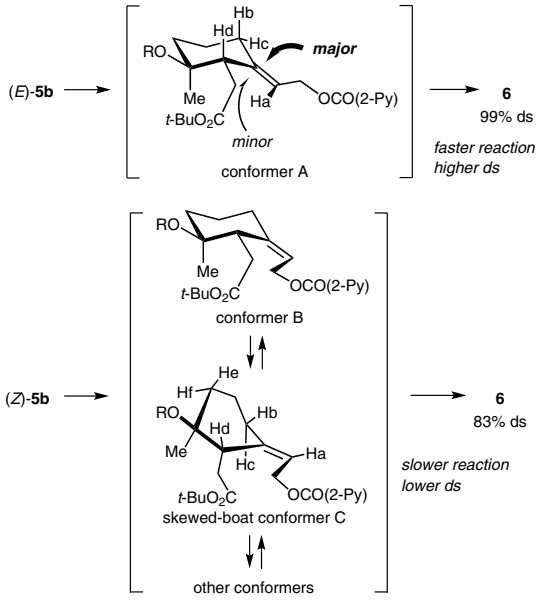
The (*E*)-**5** and (*Z*)-**5b** synthesized separately were also subjected to the substitution to compare reactivity and diastereoselectivity between the isomers using sufficient quantity of the reagent. The former was consumed almost completely within one hour, affording **6a** with 99% ds in



Scheme 5 Lactonization of the (*E*)- and (*Z*)-**5** and conversion into **1**

85% yield (Scheme 5). TMS ether **6a** was directly subjected to lactonization with *p*-TsOH·H_2O, furnishing **1** in 82% yield.[16] On the other hand, the substitution of (*Z*)-**5b** was slow at temperatures between –40 °C to –5 °C and continued at room temperature overnight, affording a mixture of **6b** (87% ds) and unidentified product(s) after the hydrolysis of the TMS ether.

The reactivity and diastereoselectivity being different between the olefin isomers might be explained using conformers A and B for the *E*- and *Z*-isomers, respectively (Scheme 6). Conformer A constitutes a stable conformer because of no severe steric obstacles, thus allowing a normal access of the methyl copper reagent from the equatorial direction. In contrast, conformer B might exist in equilibrium with other conformer(s) such as a pseudo-skewed boat conformer C[17] to release steric repulsion between the two side chains in conformer B. The axial hydrogen H_e overhanging on the allylic olefin is probably the reason for the slower reaction of (*Z*)-**5b**.



Scheme 6 Plausible conformers in the substitution of (*E*)-**5b** and (*Z*)-**5b** with the methyl copper reagent

In summary, we have developed a stereoselective synthesis of anastrephin (**1**) from commercially available ethoxy enone **7** through allylic substitution of picolinate **5b** consisting of an (*E*)- and (*Z*)-olefin stereoisomers in 5.5% yield over 15 steps with 91% ds. These results are higher than those reported for the previous syntheses of **1**.[18,19] Furthermore, we clarified that the *E* isomer of **5b** gave higher diastereoselectivity than the *Z* isomer (99% ds vs. 85% ds). The present method would spur on biological study of anastrephin.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561576.

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(14) Enantiomeric purity of **13** was calculated to be 95% ee based on 99% ee of **10** and 98% ds of **12**.

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(16) Anastrephin (**1**) prepared from (*E*)-**5** (95% ee): $[\alpha]_D^{21}$ –39 (*c* 0.37, hexane) and mp 91.5–93.0 °C. Compare ref. 3b $[\alpha]_D^{26}$ –45.1 (*c* 0.51, hexane) and mp 88.0–89.5 °C; ref. 3a $[\alpha]_D^{23.5}$ –50.4 (*c*

0.25, hexane) and mp 91.0–91.5 °C; ref. 1h $[\alpha]_D$ +48.8 (hexane) and mp 94–95 °C for *ent*-**1**. Since the $[\alpha]_D$ value of epianastrephin (**2**) is larger than **1** {$[\alpha]_D^{28}$ –72.5 (*c* 0.57, hexane)}, contamination of **2** in **1** might be a reason for the reported larger $[\alpha]_D$ value of **1**. The copy of the ^{1}H NMR spectrum of **1** attached in their Supporting Information is contaminated with **2**.[3b]

(17) This conformer is supported by ^{1}H NMR analysis: Conformer C, J_{Ha-Hb} = 1.6 Hz, J_{Hb-Hd} = 0 Hz; conformer A, J_{Ha-Hc} = J_{Hc-Hd} = 0 Hz.

(18) Lit.[3a] 0.28% yield, 23 steps, 23% ds (46% ds and 50% ds in the two steps) from geraniol; lit.[3b] 0.16% yield, 31 steps, 33% ds (53% and 63% ds in the two steps) from glucose; lit.[3c] 0.89% yield, 27 steps, 47% ds (75% and 63% ds in the two steps) from geraniol.

(19) A solution of **5b** (*E*/*Z* = 47:53, 284 mg, 0.76 mmol) in THF (2 mL) was added to a mixture of MeMgBr (0.97 M in THF, 2.60 mL, 2.52 mmol), CuBr·Me_2S (235 mg, 1.14 mmol) and ZnI_2 (392 mg, 1.23 mmol) in THF (1 mL) at –40 °C. The resulting mixture was warmed to r.t. and stirred overnight to afford olefin **6b** (105 mg, 51%, 92% ds) after chromatographic purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 3 H), 1.08 (s, 3 H), 1.27–1.35 (m, 1 H), 1.39–1.46 (m, 1 H), 1.45 (s, 9 H), 1.50–1.60 (m, 2 H), 1.73 (br s, 1 H), 1.77–1.86 (m, 2 H), 1.95 (dd, *J* = 6.0, 4.8 Hz, 1 H), 2.31 (dd, *J* = 16.4, 4.8 Hz, 1 H), 2.45 (dd, *J* = 16.4, 6.4 Hz, 1 H), 5.00 (dd, *J* = 17.6, 1.2 Hz, 1 H), 5.03 (dd, *J* = 11.2, 0.8 Hz, 1 H), 5.88 (ddd, *J* = 17.6, 11.2, 0.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (–), 22.1 (+), 28.1 (+), 30.1 (+), 31.8 (–), 37.5 (–), 41.1 (–), 43.2 (–), 53.9 (+), 73.0 (–), 80.4 (–), 112.5 (–), 142.2 (+), 174.8 (–). The diastereoselectivity of **6b** was determined by integration of the key signals in the ^{1}H NMR [δ = 5.88 (ddd) for **6b** and δ = 5.71 (dd) for the diastereomer].