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Reactions of alanes and aluminates with tri-substituted epoxides. Development of a stereospecific alkynylation at the more hindered carbon

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Abstract—The addition of 4 equiv of phenyl ethynyl dimethyl alane (formed by treatment of phenyl acetylene with *n*-BuLi followed by Me$_2$AlCl) to 2,3-epoxy geraniol results in the formation of the C-3 alkynyl addition product and the Yamamoto rearrangement/addition product, in 53 and 18% yield, respectively. Replacing the alane reagent with an aluminate (formed by treatment of phenyl acetylene with *n*-BuLi followed by Me$_3$Al) and adding BF$_3$·OEt$_2$ result in formation of the C-3 addition product in 73% yield.
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1. Introduction

Epoxides are readily accessible important synthetic building blocks for synthesis, and the development of new methods for their functionalization remains important. Recently, we reported a general method for opening unactivated tri-substituted epoxides at the more sterically congested center with alkynyl aluminates in the presence of BF$_3$·OEt$_2$ (Scheme 1).[1] With a few rare exceptions usually involving activated propargylic[2,3] or benzylic[4,5] substrates, a general method for the addition of carbanions to the more hindered position of tri-substituted epoxides was previously unknown.[6–8] In this paper we describe the discovery pathway and reaction optimization processes that lead to the optimized alkynylation conditions, and report for the first time the alkylation results from our preliminary work using alkynyl alanes. These results illuminate differences in reactivity between alanes and aluminates, and clearly show that aluminates are superior to alanes for this transformation.

2. Results and discussion

2.1. Opening of tri-substituted epoxides using alkynyl alanes

Our initial objective was to add an acetylide to the more hindered carbon of a tri-substituted epoxide to provide

a functionalized *gem*-methyl fragment that could potentially be applied to the synthesis of natural products, such as the epothilones or pelorusides. The prenyl alcohol derived epoxide **1** was one of the early model substrates examined, and it was selected in part because the alcohol functionality (or a protected version) is likely to facilitate the addition to the distal carbon as it does in reactions of di-substituted epoxides (Scheme 2).[9] Therefore, the alane reagent **2** prepared in situ from trimethylsilyl acetylene, *n*-BuLi, and dialkyl aluminum chloride was tested for the desired transformation. The dimethyl aluminum reagent showed some promise by providing the C-3 addition product **3** in 10% yield, whereas the diethyl reagent gave no desired product. In addition to the desired addition product **3**, the Yamamoto rearrangement/addition[10] product **4** and C-2 addition product **5** were isolated. The products were identified on the basis of their ¹H NMR spectra and ¹H COSY analysis (see Supplementary data). Further evidence for the C-3 addition product was obtained by oxidation to the corresponding aldehyde with sodium periodate. Once characterized, further experiments to optimize the reaction were monitored by GC and NMR in lieu of product isolation.[11]

The addition reaction was optimized by testing various solvents at different temperatures (Table 1). First, coordinating solvents, such as THF and Et$_2$O, shut down the reaction completely (entries 1 and 2). The non-coordinating solvents dichloromethane and toluene gave similar results (entries 3 and 4).[12] At lower temperatures, less amount of the Yamamoto rearrangement product **4** was produced, while the C-2 addition product **5** increased (entries 4–6).
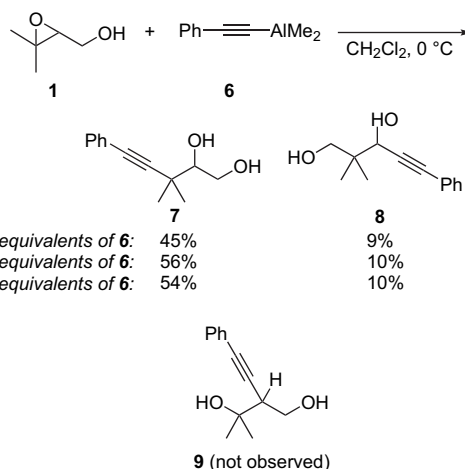
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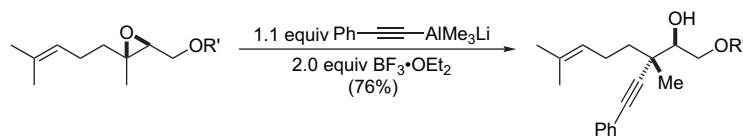
Scheme 1. Addition of alkynyl aluminates.
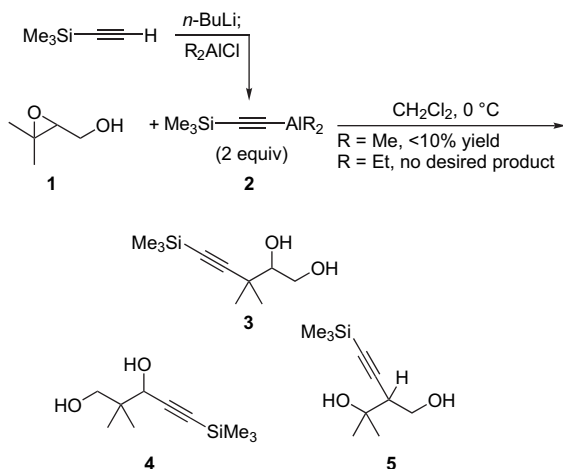
Scheme 2. Initial results on the ring opening of prenyl epoxide by alane complexes.

Scheme 3. Addition of phenyl acetylene to prenyl epoxide.

product **13**, the elimination product **14** and the C-3 chlorination product **15**. These by-products were also observed with the trimethylsilyl acetylene addition to the geraniol epoxide.

Table 1. Optimization of the epoxide ring opening employing alane reagents

| Entry	Solvent	T (°C)	Percentage in GC analysis (%)		
			3	**4**	**5**
1	THF	−78	0	0	0
2	Et$_2$O	−78	0	0	0
3	Toluene	−78	32	4	13
4	CH$_2$Cl$_2$	−78	36	3	7
5	CH$_2$Cl$_2$	−30	54	9	0
6	CH$_2$Cl$_2$	0	52 (33)[a]	16	0

[a] Isolated yield.

Using phenyl acetylene in the reaction at 0 °C gave improved results (Scheme 3), and the C-3 addition product **7** was isolated in 45% yield along with 9% of the Yamamoto rearrangement/addition product. None of the C-2 addition product was observed. Increasing the equivalents of alane **6** from 3 to 4 resulted in an improvement in isolated yield from 45 to 56%, but the yields were unchanged with 6 equiv of alane.

The above reactions suffered from poor mass recovery of about 75%, and it was suspected that water-soluble products might be getting lost during the workup, so the more hydrophobic (and sterically hindered) epoxide **10** was examined (Scheme 4). The result was an increase in total mass recovery to around 95%. Accompanying the desired C-3 alkylation product **11** and expected rearrangement by-product **12**, additional compounds from other side reactions were discovered in trace amounts, including the C-3 methylation

**Scheme 4**. Addition of phenyl acetylene to geraniol epoxide.

While we found these results informative and encouraging, one clear detraction from the method at this point in its development was the requirement for 4 equiv of the acetylene, which is inefficient and potentially problematic with synthetic intermediates or expensive alkynes. To abrogate the demand for excess alkyne, the epoxy alcohol **10** was treated with 1 equiv of Me$_3$Al or Et$_3$Al prior to addition of the alkynyl alane **6** (2 equiv) (Scheme 5); however, with either additive the isolated yields of the desired product **11** was

inferior to the previous results, and with Et$_3$Al the reaction required 5 h for completion instead of 2.5 h.
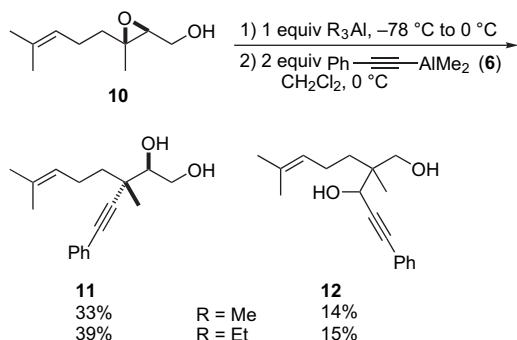
Scheme 5. Pretreatment with Me$_3$Al or Et$_3$Al.

The increase in reaction time required with the Et$_3$Al additive prompted us to explore the effect of the alkyl substituents on the alkynyl alane reagent itself (Scheme 6). After efforts at optimization similar to those described above, the best conditions identified for C-3 alkylation with diethyl alane **16** was the use of 8 equiv in CH$_2$Cl$_2$ solvent at 20 °C. The 43% yield of C-3 alkylation product **11** is lower than that from the dimethyl alane reagent (Scheme 4, 53%), and more rearrangement product was observed (28 vs 18%).
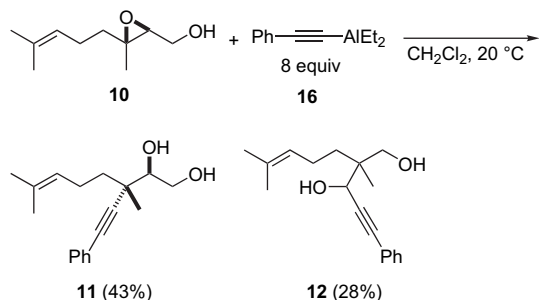
Scheme 6. Reactions with diethyl alkynyl alane.

Having settled on the dimethyl alane as the best available reagent for this transformation, additions of trimethylsilyl acetylene and 1-pentyne were screened under the standard reaction conditions of 4 equiv of the dimethyl alane at 0 °C in CH$_2$Cl$_2$ (Scheme 7). The result from addition of the silyl acetylene was a disappointing 1:1 mixture of diastereomers in 23% isolated yield (average of two runs) along
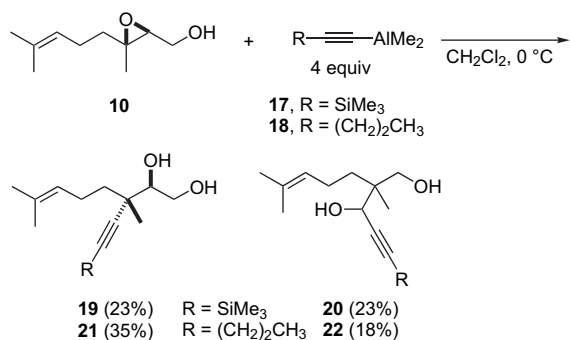

Scheme 7. Additional examples of epoxide alkylation with alane reagents.

with an equal amount of the rearrangement product (**20**), also as a 1:1 mixture of diastereomers. The lack of selectivity is likely due to steric hindrance, and reactivity problems encountered with bulky aluminates are described in the next section. Addition of 1-pentyne was comparably uninspiring at 35 and 18% for the addition and rearrangement products, respectively, but as single diastereomers. Further work on these alane additions was abandoned in favor of reactions with aluminates.

2.2. Opening of tri-substituted epoxides using aluminates

The ability of the alkynyl alanes to alkylate at the more hindered carbon of a tri-substituted epoxide was interesting, but the requirements for excess alkyne coupled with poor yields rendered the technique unsuitable as a general methodology. It had been reported that weakly nucleophilic alkenyl and alkynyl aluminates can be coaxed to react with di-substituted epoxides when activated by BF$_3$·Et$_2$O.[13] This approach was then examined with phenyl acetylene and epoxide **10** (Scheme 8). The aluminate was simply generated in situ by deprotonation of the alkyne with n-BuLi followed by addition of Me$_3$Al. It should be noted that no experimental evidence has been obtained to help to ascertain the exact nature of the nucleophile, specifically whether it is an aluminate or not, and that the description of the nucleophile as an aluminate is based on stoichiometry and the propensities of migration of unsaturated groups over aliphatic ones under 'aluminate conditions'.[14] None the less, this reagent combination was unreactive toward epoxide **10** at 0 °C, but underwent addition at −50 °C in the presence of BF$_3$·Et$_2$O to give the desired C-3 addition product **11** in 55% yield. For an initial experiment these results were quite promising in that only 2 equiv of the aluminate was employed, the yield matched the best results ever obtained under the optimized alane conditions and none of the rearrangement product **12** was observed.
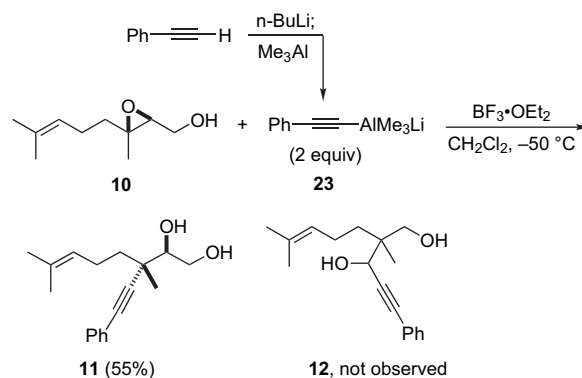

Scheme 8. Preliminary reaction with an aluminate.

A benzyl ether protected geraniol epoxide was then evaluated to determine whether the reaction would succeed with only 1 equiv of aluminate (Table 2), and in the reaction with the phenyl acetylene derived reagent, a 61% isolated yield of C-3 addition product was obtained.[15] The aluminates from 1-pentyne (entry 2) and a propargyl ether (entry 3) also performed well, affording the C-3 addition products in 54 and 57% yield, respectively. Curiously, reaction with the trimethylsilyl acetylene derived aluminate gave only trace amounts of addition product (entry 4).

Table 2. Preliminary reactions with 1 equiv of aluminate
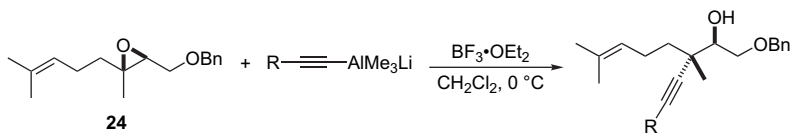
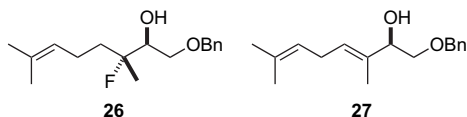| Entry	R	Yield (%)
1	Ph	61
2	$CH_3CH_2CH_2$	54
3	$TBSOCH_2$	57
4	$SiMe_3$	<10

Table 3. Optimization of the epoxide ring opening reaction using aluminates
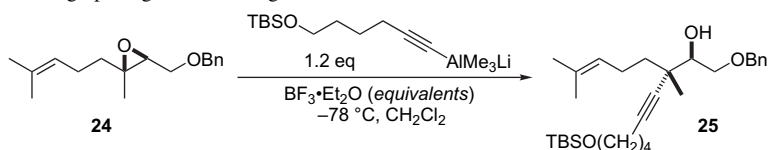
| Entry	$BF_3 \cdot Et_2O$ (equiv)	Concentration (M in epoxide)	Yield (%)
1	1	0.04	52
2	2	0.04	54
3	4	0.04	55
4	1	0.12	66
5	2	0.12	78

Under these unoptimized reaction conditions, conversion was low and other Lewis acids such as $Ti(O^iPr)_4$ and $(MeO)_3B$ were screened. However, these acids gave less satisfactory results, and attention was given to optimizing the reaction using $BF_3 \cdot Et_2O$ (Table 3). It was found that in 0.04 molar solution, the reaction was insensitive to the equivalents of $BF_3 \cdot Et_2O$ (entries 1–3), but at higher concentration

(01.12 M) 2 equiv was found to be ideal, giving the desired product in a reproducible 78% isolated yield (entries 4 and 5).

Under the best reaction conditions identified in Table 3 (entry 5), the only by-products formed in suitable quantity (<5%) for characterization were the C-3 fluorination and elimination products **26** and **27** (Chart 1). In strong contrast to the alane reactions, Yamamoto rearrangement products were only observed in rare cases and in negligible amounts.

The current protocol is quite tolerant to variations in both the nucleophilic acetylene and the protecting groups on the epoxy alcohol (Table 4). For example, the benzyl and TBS ethers as well as substrates with free alcohols give similar

Chart 1. By-products in the aluminate reaction.

Table 4. Ring opening of geraniol epoxide with different terminal alkynes
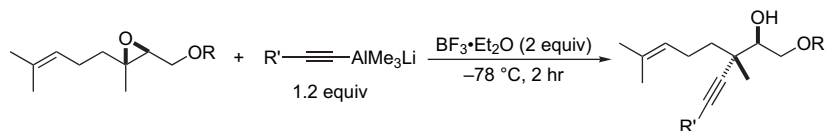
Entry	R	R'	Yield (%)
1	Bn	Ph	89
2	TBS	Ph	76
3[a]	H	Ph	61
4	Bn	$TBSO(CH_2)_4$	81
5	TBS	$TBSOCH_2$	67
6	Bn	$CH_3CH_2CH_2$	72
7	Bn	p-MeO-C_6H_4	77
8	Bn	Me-C_6H_4	74
9	Bn	p-F-C_6H_4	67
10	Bn	$SiMe_3$	35
11	Bn	H	45

[a] Aluminate of 2.2 equiv was used.

results (entry 1–3). Terminal alkynes with ethereal functional groups can be used as nucleophile (entries 4 and 5). The pentyne-derived reagent opened the epoxide in 72% yield (entry 6). Entries 7–9 show that the efficiency of the reaction is unaffected by the electronic properties of the incoming nucleophiles. However, apart from these promising results, it was found that trimethylsilyl acetylene cannot be added efficiently (entry 10), and the isolated yield for the C-3 addition product was only 35%. This is disappointing in that desilylation of the alkyne gives access to a new terminal acetylene for further functionalization. In another approach to gain access to free alkyne product, acetylene itself was employed[16] and this successfully gave the product in 45% isolated yield (entry 11).[17] The lack of reactivity for trimethylsilyl acetylene in both alane and aluminate reactions is ascribed to the size of the trimethylsilyl group, and in this regard triisopropylsilyl acetylene and 2-methyl-3-butyn-1-ol failed to react at all. The incompatibility with bulky alkynyl nucleophiles appears to be the main limitation of this synthetic method.

It was found that Me$_3$Al can be used in sub-stoichiometric quantities, but the yield is diminished (Scheme 9). Specifically, under the standard reaction conditions (employing 1.2 molar equivalents of Me$_3$Al), the aluminate derived from enyne **28** afforded the C-3 alkylation product in 85% isolated yield. Decreasing the amount of Me$_3$Al to 0.1 equiv, while keeping the other conditions the same, gave a 55% yield of **28**. In the absence of Me$_3$Al there is no reaction.
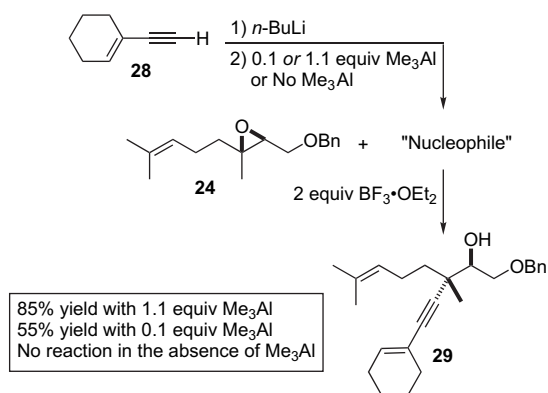
**Scheme 9**. Epoxide ring opening by aluminates using catalytic amount of Me$_3$Al.

This alkynylation reaction has proven to be remarkably general in regard to epoxide substrates (Table 5). The reaction performs equally well with epoxides derived from allylic alcohols (entries 1–3), including cyclohexenols (entry 3), as it does with epoxides prepared from non-functionalized olefins (entries 4–6).

Because both 2,3-epoxy ethers and non-activated epoxides react with the alkynyl aluminate reagents with comparable efficiency, a competition study was performed to see which class of substrates will react faster (Scheme 10). In the event, epoxides **30** and **31** were treated with aluminate **23** under the standard reaction conditions (except that 0.9 equiv of aluminate were employed instead of 1.2 equiv). A 75% yield of **33**

Table 5. Additional scope of the epoxide opening reaction

Entry	Epoxide	Product	Yield (%)
1			92
2			50
3			89
4			93
5			76
6			70

from preferential addition to the non-functionalized epoxide was obtained and 90% of epoxide **32** was recovered from the reaction.
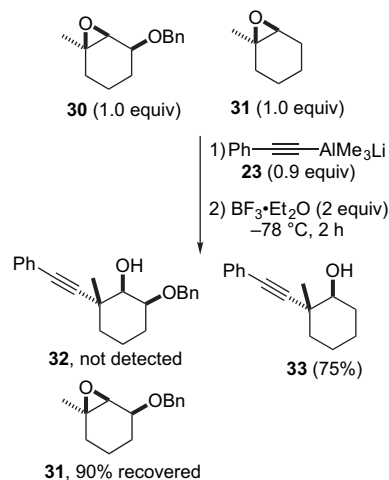
Scheme 10. Competing reaction of 2,3-epoxy alcohols and non-activated epoxides.

The stereochemistry of the reaction is an obvious concern, and evidence for clean inversion of stereochemistry (implying S$_N$2 like backside attack) at the epoxide was described

in the initial communication. As there is no new information available on this topic, those results will not be repeated here.[1]

3. Conclusion

A protocol for the stereospecific addition of terminal alkynes at the more hindered carbon of tri-substituted epoxides using aluminates was developed that provides a practical solution to a long standing problem in epoxide chemistry. The reaction provides products with regiochemistry complimentary to that obtained by steric control.[18] This full report provides additional insight into the reactivity of tri-substituted epoxides with alkynyl alanes and aluminates and highlights important reactivity differences.

4. Experimental section

4.1. General procedure for the addition of alanes

3,3-Dimethyl-5-trimethylsilanyl-pent-4-yne-1,2-diol (**3**):[6] to a 0 °C solution of trimethylsilyl acetylene (0.18 mL, 1.2 mmol) in hexanes (3 mL) was added *n*-BuLi (0.41 mL, 1.1 mmol, 2.54 M solution in hexanes) dropwise followed by Me$_2$AlCl (0.83 mL, 0.83 mmol, 1.0 M solution in hexanes) 30 min later. After 30 min, the resulting mixture was allowed to warm to room temperature and stirred for an additional 30 min. To a 0 °C solution of epoxy prenol (0.03 mL, 0.28 mmol) in CH$_2$Cl$_2$ (3 mL) was added the thus obtained alane solution. When the reaction was complete (TLC, 2.5 h), 10% v/v HCl solution (10 mL) was added at 0 °C. The organic phase was separated and the aqueous solution was extracted with EtOAc (2×10 mL). Concentration of the combined organic layers and purification of the residual yellow oil by chromatography on silica gel (30% EtOAc/hexanes for elution) afforded a white solid (18 mg, 33%): R_f 0.41 (50% EtOAc/hexanes); ^{1}H NMR (600 MHz, CDCl$_3$): δ 3.82–3.79 (m, 1H), 3.65 (dd, J=11.4, 7.8 Hz, 1H), 3.42–3.40 (m, 1H), 2.33 (br, 2H), 1.25 (s, 3H), 1.20 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 110.8, 86.9, 77.5, 63.5, 35.8, 25.5, 0.1. HRMS *m/z*: 201.1309 (calcd for C$_{10}$H$_{21}$O$_2$Si [M+H]$^+$: 201.1311).

4.2. General procedure for the addition of aluminates

(2*S*,3*S*)-1-Benzyloxy-3,7-dimethyl-3-phenylethynyl-oct-6-en-2-ol (Table 4, entry 1):[1] to a 0 °C solution of alkyne (1.2 mmol) in Et$_2$O (5 mL) were added *n*-BuLi (1.2 mmol, 2.6 M in hexane) and Me$_3$Al (1.1 mmol, 2.0 M in toluene). The resultant mixture was allowed to warm to room temperature, the epoxide was added, the solution was cooled to −78 °C, and BF$_3$·Et$_2$O (2.0 mmol) was added dropwise. When the reaction was complete (TLC, 1.5 h), dry MeOH (1.0 mL) was added and after 15 min, the resulting mixture was poured into 0 °C pH 10 NaHCO$_3$/NaOH buffer (20 mL). Purification by flash chromatography on SiO$_2$ with 12% EtOAc/hexanes for elution gave the desired product as a yellow oil (163 mg, 89%): R_f 0.33 (15% EtOAc/hexanes); IR (thin film): ν 3700–3150, 2976, 2933, 2871, 2338 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35–7.25 (m, 10H), 5.15 (t, J=7.2 Hz, 1H), 4.58 (s, 2H), 3.82 (dd, J=9.6, 2.8 Hz, 1H), 3.77 (dd, J=8.8, 2.4 Hz, 1H), 3.63 (dd, J=8.0, 8.0 Hz, 1H), 2.25–2.10 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.73–1.51 (m, 2H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.0, 131.7, 131.6, 128.4, 128.1, 127.7, 124.2, 123.5, 93.1, 83.5, 75.8, 73.4, 71.6, 39.4, 37.1, 25.7, 23.5, 22.7, 17.6; HRMS *m/z*: 363.2316 (calcd for C$_{25}$H$_{31}$O$_2$ [M+H]$^+$: 363.2324).

Supplementary data

Tabulated ^{1}H NMR and ^{13}C NMR data and other characterization data of all new products. Copies of ^{1}H NMR and ^{13}C NMR spectra. This material available free of charge via the Internet at http://acs.pubs.org. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.036.

References and notes

1. Zhao, H.; Pagenkopf, B. L. *Chem. Commun.* **2003**, 2592–2593.
2. Balasubramaniam, R. P.; Moss, D. K.; Wyatt, J. K.; Spence, J. D.; Gee, A.; Nantz, M. H. *Tetrahedron* **1997**, *53*, 7429–7444.
3. For a recent example, see: Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900–13901.
4. (a) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734–2743; (b) Jansen, R.; Knopp, M.; Amberg, W.; Bernard, H.; Koser, S.; Müller, S.; Münster, I.; Pfeiffer, T.; Riechers, H. *Org. Process Res. Dev.* **2001**, *5*, 16–22.
5. For a recent example, see: Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711–7714.
6. For examples with Nagata's reagents, see: Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1999**, *40*, 1041–1044.
7. For an example with a cuprate, see: Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Org. Chem.* **1988**, *53*, 4274–4282.
8. Similar products by other methods, see: Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944–5951; Saito, T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757–10758; Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949–8950; Ishibashi, N.; Masahiro, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 3775–3778.
9. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560; For other examples, see: (b) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597–3600; (c) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377–1380; (d) Ahn, K. H.; Kim, J. S.; Jin, C. S.; Kang, D. H.; Han, D. S.; Shin, Y. S.; Kim, D. H. *Synlett* **1992**, 306–308; (e) Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71–72.
10. (a) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432; (b) Maruoka, K.; Murase, N.; Bureau, R.;

Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663–3672; (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303–3312 and the references therein.

11. Isolated yields do not add to 100% as other unidentified species were present.

12. Benzene, chloroform, dichloroethane and various mixtures of these solvents gave similar results.

13. (a) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 6197–6202; (b) Skrydstrup, T.; Benechie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1990**, *31*, 7145–7148.

14. Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* **2002**, *4*, 4735–4737.

15. It is worth noting that reaction of epoxy ether **24** under the optimized alane conditions gave the C-3 addition product in 57% yield, and 54% yield if $BF_3 \cdot OEt_2$ was added.

16. Midland, M. M.; McLoughlin, J. I.; Werley, R. T. J. *Org. Synth.* **1990**, *68*, 14–24.

17. Due to the technical difficulties of forming lithium acetylide from acetylene gas and *n*-BuLi, this yield should be considered unoptimized.

18. (a) Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2285–2287; Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, 877–880; (b) Lee, D.-H.; Rho, M.-D. *Tetrahedron Lett.* **2000**, *41*, 2573–2576.