HETEROCYCLES, Vol. 80, No. 2, 2010, pp. 1449 - 1456. © The Japan Institute of Heterocyclic Chemistry
Received, 10th July, 2009, Accepted, 4th September, 2009, Published online, 4th September, 2009
DOI: 10.3987/COM-09-S(S)50

STEREOSELECTIVE PREPARATION OF OXYGENATED HETEROCYCLES USING STEREOCONTROLLED TANDEM DOUBLE-ALLYLATION OF CARBONYL COMPOUNDS WITH A BORON-SILICON REAGENT

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Abstract – A one-pot three-component reaction between carbonyl double-allylation reagent **1** and aldehydes was optimized to provide a high diastereoselectivity in the formation of all-*cis* trisubstituted tetrahydrofurans. A similar procedure applied to dicarbonyl substrates provided an oxabicyclic compound embedding an 8-membered medium ring.

Saturated oxygen-containing heterocycles such as tetrahydrofurans and pyrans are key components of numerous natural products and pharmaceutical drugs.[1] There is a need to develop rapid means for synthesizing these important classes of heterocycles from simple components.[1] In this regard, we have recently developed the carbonyl double allylation reagent **1**, which is based on boron and silicon (Figure 1).[2,3] This optically pure reagent adds onto aldehydes first via an allylboration (transition state **2**), to give a secondary alcohol product, **3**, with concomitant unmasking of an allylic silane (Eq. 1). The allylic silane unit of **3** can then react chemoselectively with a second aldehyde to provide all-*cis* trisubstituted tetrahydrofurans **5** through cyclization onto oxonium intermediate **4**.[4]

‡Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

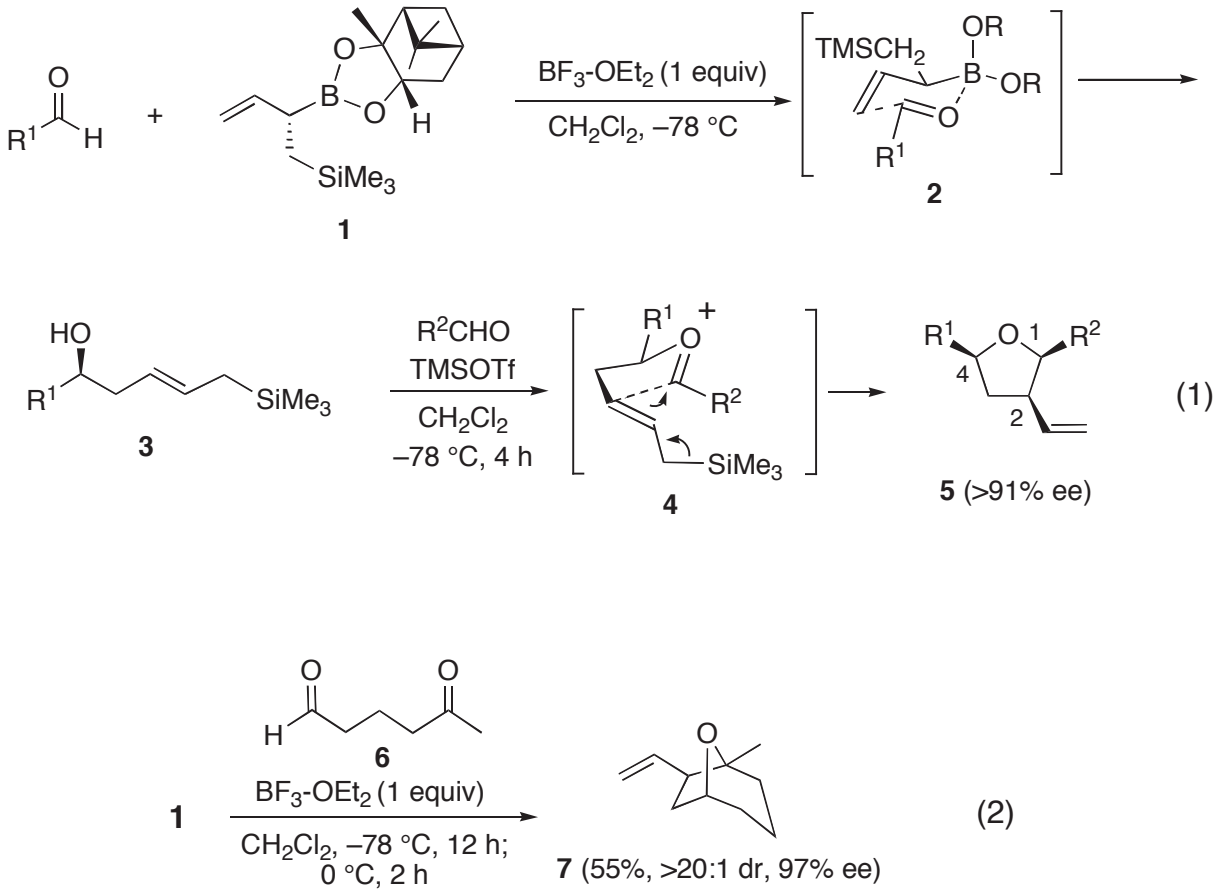
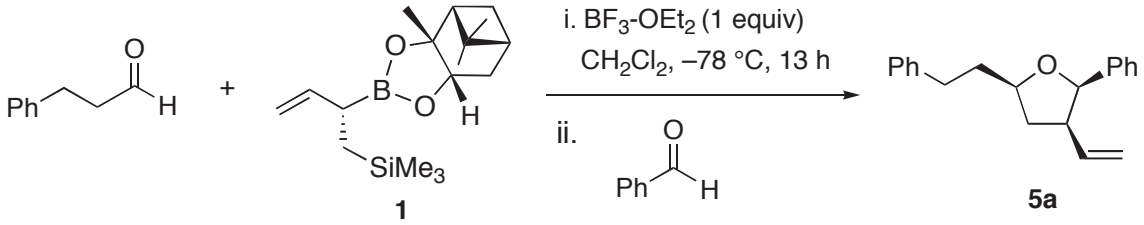


Figure 1. Preparation of trisubstituted tetrahydrofurans and oxabicyclic compounds using carbonyl double-allylation reagent **1**.

In our initial studies, we found that the diastereoselectivity of this process was higher when performed in two distinct steps with isolation of allylic silanes **3**. Although a one-pot sequential addition of two aldehydes afforded the desired products in excellent enantioselectivity, the diastereoselectivity was notably lower compared to the two-step process.[2] When using the one-pot procedure with a final temperature of 0 °C, a significant proportion of 1,2-*trans* diastereomer was observed. In a related application, we showed one example where a ketoaldehyde, **6**, can be utilized to promote first an intermolecular allylboration, then an intramolecular allylsilation[5] that provides oxabicyclic product **7** embedding a 7-membered carbocycle. As such, it became apparent that this approach could be useful in providing medium rings following an opening of the oxygen bridge. Thus, in this study our objective was twofold: 1. Develop a highly diastereoselective one-pot three-component reaction procedure to prepare trisubstituted tetrahydrofurans **5** from reagent **1** and two different aldehydes, and 2. Expand this procedure to the use of dicarbonyl substrates as a means to access medium ring systems.

The optimization of a one-pot three-component procedure for tetrahydrofurans **5** focused on identifying the optimal reaction temperature for the second aldehyde allylation. Thus, using hydrocinnamaldehyde as the first aldehyde substrate with reagent **1** and boron trifluoride etherate at –78 °C,[6] benzaldehyde was added as the second aldehyde at this temperature. The final temperature at which the solution was warmed up to was varied and the yield and diastereoselectivity in the formation of 1,2,4-trisubstituted tetrahydrofuran **5a** was assessed (Table 1). Although a temperature of 0 °C led to a shorter reaction time, the resulting diastereoselectivity ratio of 7:1 was disappointing (entry 1). On the other hand, maintaining the temperature of the second allylation at lower temperatures led to a higher stereoselectivity (entry 2). When reacted at –40 °C for 20 hours, the model reaction afforded a single diastereomer, however in a low yield of 40% (entry 3). Increasing the reaction time to 48 hours led to an appreciable increase of the yield of **5a** with excellent diastereoselectivity (entry 4). None of the 1,2-*trans* diastereomer was observed in the crude product, and the desired all-cis product **5a** was obtained in 91–94% ee. Using these optimal conditions, a few more examples of products were compiled to ascertain the reproducibility and reliability of this procedure. Thus, all-*cis* trisubstituted tetrahydrofurans **5a**-**5c** were all obtained in very high diastereoselectivity (Figure 2). In the case of **5c**, 3-*tert*-butyldimethylsiloxy propanal was employed as the starting aldehyde but the TBS protecting group was removed either during the work-up and the purification on silica column.

Table 1. Optimization of a one-pot three-component preparation of tetrahydrofurans.[a]



entry	temp and time for step ii	yield % [b]	dr of **5a** [c]
1	–78 °C, 2 h ; 0 °C, 4 h	50	7:1
2	–78 °C, 1 h ; –20 °C, 20 h	50	16:1
3	–78 °C, 1 h ; –40 °C, 20 h	40	>20:1
4	–78 °C, 1 h ; –40 °C, 48 h	60	>20:1

[a] Reaction conditions: 0.50 mmol of **1** and 0.50 mmol of hydrocinnamaldehyde were stirred with 0.50 mmol of BF_3•OEt_2 at 0.1–0.2 M, followed by benzaldehyde (0.50 mmol). [b] Isolated yields. [c] Measured by ^{1}H NMR on crude reaction products. The all-*cis* stereochemistry of the major diastereomer was proved using nOe experiments.[2] The minor diastereomer has a 1,2-*trans* stereochemistry.

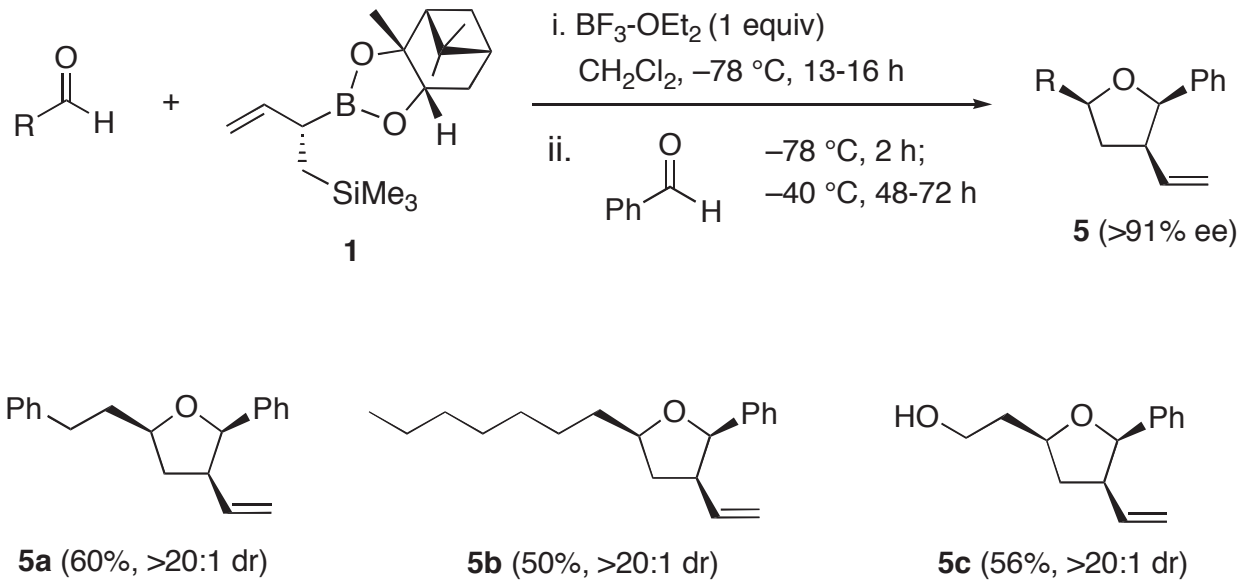
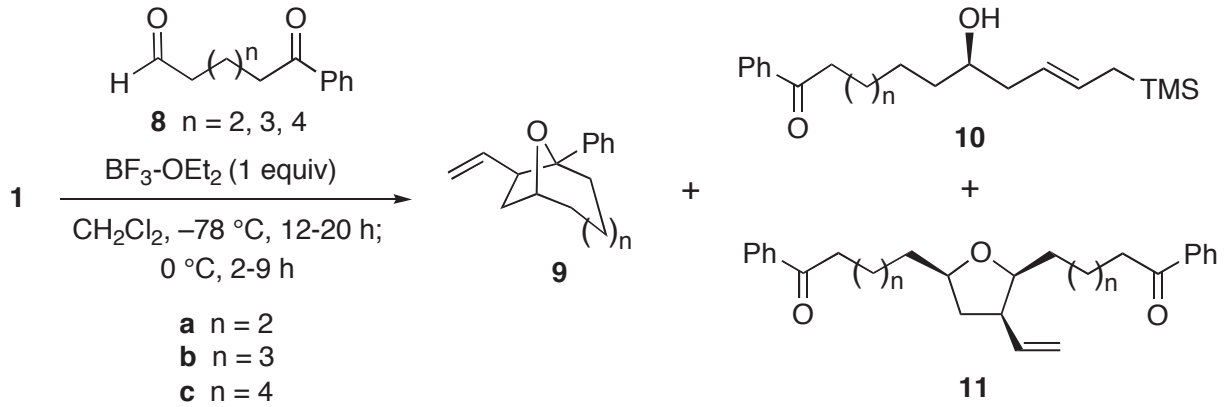


Figure 2. One-pot three-component preparation of trisubstituted tetrahydrofurans **5a**-**5c**.

The application of this one-pot double allylation procedure was evaluated with a series of dicarbonyl substrates to explore the limits of this method as a means to access medium ring, oxygen-bridged carbocycles. In our previous study, a 7-membered carbocycle was made successfully (Figure 1, Eq. 2).[2] Ketoaldehydes were chosen so as to minimize intermolecular allylation for the allylsilation, which, as the second allylation, will occur on the phenylketone. The first allylation with the allylic boronate unit is expected to occur on the aldehyde, and the second allylation on the hindered phenylketone should be slow despite its intramolecular nature. Using reagent **1** and the shortest dicarbonyl substrate, keto-aldehyde **8a**, we first examined conditions similar to the above tetrahydrofurans, at normal concentration (Table 2). Unfortunately, at 0.1 M concentration, none of the desired product **9a** was obtained (entry 1). The difficult intramolecular ketone allylation is evident by the isolation of 60% of product **11a**, which originates from a second, intermolecular allylation on the aldehyde unit of **8a**. It was expected that this undesired product could be suppressed by working at a lower concentration that would disfavor the intermolecular process. In the event, diluting the reaction concentration down to 0.004 M led to a 60% yield of the desired product **9a** with only 10% of side-product **11a** (entry 3). Remarkably, product **9a** embeds an 8-membered carbocycle. These conditions, however, failed to deliver the 9- and 10-membered carbocycles with the longer ketoaldehydes **8b** and **8c** (entries 4-5).

Table 2. Optimization of a one-pot preparation for medium-ring oxabicyclic compounds.[a]



entry	ketoaldehyde	conc. (M)	yields % [b]		
			9	**10**	**11**
1	**8a**	0.1	0	35	60
2	**8a**	0.01	40	0	30
3	**8a**	0.004	60	0	10
4	**8b**	0.004	0	55	20
5	**8c**	0.004	0	12	65

[a] Reaction conditions: equimolar amounts of **1** and ketoaldehyde were stirred with 1.5 equivalent of $BF_3.OEt_2$ at the indicated concentration. [b] Isolated yields.

In summary, by employing carbonyl double-allylation reagent **1**, a one-pot three-component synthesis of all-*cis* trisubstituted tetrahydrofurans was optimized to provide a high enantio- and diastereoselectivity. Using a dicarbonyl substrate in a similar procedure under dilute conditions, an oxabicyclic compound embedding an 8-membered medium ring was isolated in good yield. Carbocycles of this sort are difficult to obtain using other methods. Overall, these results further expand the versatility of boron-silicon double-allylation reagent **1**. Applications to the synthesis of biologically active natural products are underway.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere using flame-dried glassware. CH_2Cl_2, methanol, and toluene were distilled over CaH_2. THF was distilled over sodium/benzophenone. All aldehydes were purified by Kugelrohr distillation prior to use.

One-pot three-component syntheses of all-*cis* trisubstituted tetrahydrofurans 5a-5c

General procedure: In a reaction vessel, the aldehyde R^1CHO (0.50 mmol) and reagent **1** (0.50 mmol) in 3 mL of CH_2Cl_2 were mixed and cooled to –78 °C. Next, $BF_3{\cdot}Et_2O$ (0.50 mmol) was added and the

mixture was stirred at –78 ºC for 13–16 h. Then, benzaldehyde (0.50 mmol) was added and stirred at –78 ºC for 2 h at –78 ºC. Thereafter, the reaction mixture was warmed to –40 ºC (same bath) and stirred for 24–72 h at –40 ºC. The reaction mixture was quenched with sat. aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O (4 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotary evaporator. The all-*cis* stereochemistry of the products was proved using nOe experiments.[2]

2-Phenyl-5-(2'-phenylethyl)-3-vinyltetrahydrofuran 5a

Preparation of this compound was described previously.[2] Analytical data of product **5a** was identical to that reported in this reference.

5-Heptyl-2-phenyl-3-vinyltetrahydrofuran 5b

The reaction scale was 0.45 mmol. Flash chromatography (0–5% EtOAc in hexanes) provided a clear liquid (66 mg, 50% yield). TLC (25% EtOAc in hexanes, phosphomolybdic acid/Ce(IV)sulfate/aq. H_2SO_4): R_f 0.69; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.20 (m, 5H), 5.18 (ddd, J = 9.0, 10.2, 17.1 Hz, 1H), 5.05 (d, J = 8.2 Hz, 1H), 4.90 (ddd, J = 0.8, 2.0, 17.0 Hz, 1H), 4.76 (dd, J = 2.1, 10.2 Hz, 1H), 4.02 (qd, J = 6.0, 9.3 Hz, 1H), 3.18 (p, J = 8.4 Hz, 1H), 2.20 (ddd, J = 5.4, 7.5, 12.3 Hz, 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.40-1.25 (m, 11H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 138.7, 127.7, 126.9, 126.8, 114.7, 83.1, 79.6, 48.9, 38.3, 35.6, 31.8, 30.0, 29.3, 26.5, 22.7, 14.1; IR ($CDCl_3$, cast film): cm^{-1} 3067, 3030, 2956, 2928, 2857, 1730, 1641, 1494, 1454, 1359, 1110, 1095, 995, 912, 721, 698; HRMS (ES, *m/z*) calculated for $C_{19}H_{28}ONa$: 295.2032, found: 295.2032 [$(M+Na)^+$].

2-(5-Phenyl-4-vinyltetrahydrofuran-2-yl)ethanol 5c

The alcohol was protected with a TBS in the starting aldehyde, but it was removed during the workup or the purification on silica column. The reaction scale was 0.43 mmol. Flash chromatography (10–80% EtOAc in hexanes) provided a yellow liquid (58 mg, 56 % yield). TLC (50% EtOAc in hexanes, $KMnO_4$ stain): R_f 0.50; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 2H), δ 7.21 (m, 3H), δ 5.18 (ddd, J = 8.7, 9.9, 17.1 Hz, 1H), δ 5.09 (d, J = 8.4 Hz, 1H), 4.92 (ddd, J = 0.9, 2.0, 17.1 Hz, 1H), 4.78 (ddd, J = 0.8, 2.0, 9.9 Hz, 1H), 4.22 (m, 1H), 3.89 (q, J = 5.4 Hz, 2H), 3.18 (p, J = 8.7 Hz, 1H), 2.60 (t, J = 5.4, 1H), 2.23 (ddd, J = 5.4, 7.2, 12.3 Hz, 1H), 2.02 (m, 2H), 1.65 (td, 9.3, 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.9, 138.1, 127.9, 127.1, 126.7, 115.3, 83.7, 79.3, 62.0, 48.4, 38.6, 37.5; IR ($CHCl_3$, cast film): cm^{-1} 3388, 3076, 3029, 2929, 2878, 1641, 1604, 1493, 1453, 1068, 914, 752, 722, 699; HRMS (ES, *m/z*) calculated for $C_{14}H_{18}O_2Na$: 241.1199, found: 241.1195 [$(M+Na)^+$].

Synthesis of oxabicyclic compound 9a: 9-Oxa-1-Phenyl-8-vinylbicyclo[4.2.1]nonane

In a 250 mL round bottom flask, ketoaldehyde **8a** (126 mg, 0.66 mmol, 1.05 equiv) and reagent **1** (193 mg, 0.63 mmol, 1.00 equiv) in 150 mL of CH_2Cl_2 were mixed and cooled to –78 ºC and stirred for 30 minutes. Next, $BF_3{\cdot}Et_2O$ (0.13 mL, 1.00 mmol, 1.50 equiv) was added to the flask and stirred for 12 h at –78 ºC, followed by 9 h at 0 ºC (different bath). The reaction mixture was quenched with sat. aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O (4 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed by rotary evaporator. Flash chromatography (0–5% EtOAc in hexanes) provided a clear oil (85.0 mg, 60.0% yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.69; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (dd, J = 1.4, 8.5 Hz, 2H), 7.31 (m, 3H), 5.99 (ddd, J = 7.3, 10.2, 17.5 Hz, 1H), 5.15 (ddd, J = 1.0, 1.9, 10.3 Hz, 1H), 5.00 (ddd, 1.2, 1.9, 17.0 Hz, 1H), 4.70 (m, 1H), 3.02 (dt, J = 5.1, 8.2 Hz, 1H), 2.71 (q, J = 9.9 Hz, 1H), 2.44 (td, J = 9.4, 12.9 Hz, 1H), 2.10 (m, 3H), 1.72 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.4, 136.7, 128.1, 126.1, 124.9, 117.7, 87.0, 76.6, 56.1, 44.5, 38.4, 34.7, 25.1, 24.9; IR ($CDCl_3$, cast film): cm^{-1} 3077, 3026, 2927, 2859, 1638, 1602, 1492, 1470, 1446, 1350, 1095, 1072, 1013, 914, 753, 700; HRMS (EI, *m/z*) calculated for $C_{16}H_{20}O$: 228.1514, found: 228.1515 [M^+]. HPLC: Chiralcel OD (0.46 cm i.d. x 25 cm), 5% *i*-PrOH/hexanes, 0.50 mL/min., UV detection at 210 nm, major peak at 7.1 min., minor peak at 8.5 min., 93% ee. A small quantity of **11a**, 5-[5-(5-Oxo-5-phenyl-pentyl)-3-vinyl-tetrahydro-furan-2-yl]-1-phenyl-pentan-1one, was also isolated. Flash chromatography (0–5% EtOAc in hexanes) yielded a white gel (28 mg, 10 % yield). TLC (25% EtOAc in hexanes, magic stain): R_f 0.39; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (m, 4H), 7.55 (m, 2H), 7.46 (m, 4H), 5.74 (ddd, J = 9.0, 9.3, 18.0 Hz, 1H), 5.00 (d, J = 5.2 Hz, 1H), 4.97 (s, 1H), 3.79 (m, 2H), 2.97 (q, J = 8.4 Hz, 4H), 2.81 (m, 1H), 2.19 (ddd, J = 6.8, 8.0, 15.8 Hz, 1H), 1.76 (m, 5H), 1.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.3, 138.7, 137.1, 132.8, 128.5, 128.0, 115.0, 81.3, 78.4, 46.7, 38.5, 38.3, 36.2, 31.6, 26.2, 24.5; IR ($CDCl_3$, cast film): cm^{-1} 3066, 2936, 2862, 1686, 1598, 1449, 1224, 1002, 752, 691; HRMS (ES, *m/z*) calculated for $C_{28}H_{34}O_3Na$: 441.2400, found: 441.2402 [$(M+Na)^+$]. $[\alpha]^{25}_D$ 16.61 (c = 0.92, $CHCl_3$).

ACKNOWLEDGMENTS

The authors are grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada for financial support of this research.

REFERENCES

1. a) M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2301; b) J. P. Wolfe and M. B. Hay, *Tetrahedron*, 2007, **63**, 261.
2. F. Peng and D. G. Hall, *J. Am. Chem. Soc*., 2007, **129**, 3070.

3. For other examples of carbonyl double allylation reagents, see: a) W. R. Roush and P. T. Grover, *Tetrahedron Lett*., 1990, **31**, 7567; b) A. G. M. Barrett and J. W. Malecha, *J. Org. Chem*., 1991, **56**, 5243; c) W. R. Roush and P. T. Grover, *Tetrahedron*, 1992, **48**, 1981; d) J. A. Hunt and W. R. Roush, *J. Org. Chem*., 1997, **62**, 1112; e) W. R. Roush, A. N. Pinchuk, and G. C. Micalizio, *Tetrahedron Lett*., 2000, **41**, 9413; f) A. G. M. Barrett, D. C. Braddock, P. D. de Koning, A. J. P. White, and D. J. Williams, *J. Org. Chem*., 2000, **65**, 375; g) E. M. Flamme and W. R. Roush, *J. Am. Chem. Soc*., 2002, **124**, 13644; h) J. H. Smitrovich and K. A. Woerpel, *Synthesis*, 2002, 2778; i) T. K. Sarkar, S. A. Haque, and A. Basak, *Angew. Chem. Int. Ed*., 2004, **43**, 1417.
4. a) P. Mohr, *Tetrahedron Lett*., 1993, **34**, 6251; b) J. H. Cassidy, S. P. Marsden, and G. Stemp, *Synlett*, 1997, 1411; c) C. Meyer and J. Cossy, *Tetrahedron Lett*., 1997, **38**, 7861.
5. a) I. E. Markó and A. Mekhalfia, *Tetrahedron Lett*., 1992, **33**, 1799; b) M. Suginome, T. Iwanami, Y. Ito, *J. Org. Chem*., 1998, **63**, 6096; c) M. Suginome, T. Iwanami, and Y. Ito, *Chem. Commun*., 1999, 2537.
6. a) L. Carosi and D. G. Hall, *Angew. Chem. Int. Ed*., 2007, **46**, 5913; b) D. G. Hall, *Synlett*, 2007, 1644.