JOC*Note*

Practical Ruthenium-Catalyzed Cyclocarbonylation of Allenyl Alcohols in 2,4,6-Collidine Leading to α,β-Unsaturated Lactones: Concise Stereoselective Synthesis of (+)-Isomintlactone

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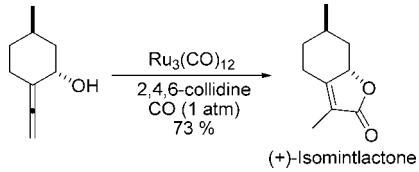

We have found that ruthenium-catalyzed cyclocarbonylation of allenyl alcohols in 2,4,6-collidine under atmospheric pressure of carbon monoxide smoothly proceeds to afford α,β-unsaturated five- and six-membered lactones in moderate to good yields. Furthermore, we have completed a highly stereoselective synthesis of (+)-isomintlactone by the cyclocarbonylation of allenyl alcohol using 2,4,6-collidine.

α,β-Unsaturated five- to seven-membered lactones not only constitute a structural feature common to numerous biologically active natural products,[1] but also have been employed as useful building blocks in organic synthesis.[2] There are a large number of synthetic methods for the α,β-unsaturated lactones,[3] among which representatives include oxidative *syn*-elimination of α-phenylseleno lactones,[3a] cycloisomerization of γ-keto carboxylic acids,[3b] cyclic carbometalation of alkynes,[3c] and RCM reaction of allyl acrylates.[3d] Recently, Takahashi et al. have reported an alternative synthetic strategy via ruthenium-catalyzed cyclocarbonylation of allenyl alcohols,[4] in which allenyl alcohols could react at 100 °C under CO (10 atm) to give α,β-unsaturated lactones.

During the course of the synthetic studies toward bipinnatin J, we studied the conversion of highly functionalized allenyl alcohol to α,β-unsaturated five-membered lactone, a γ-butenolide, using ruthenium-catalyzed cyclocarbonylation.[5] We successfully obtained the γ-butenolide, which constitutes a formal synthesis of bipinnatin J. Since ruthenium-catalyzed cyclocarbonylation is an efficient method for the synthesis of α,β-unsaturated lactones, the application of ruthenium-catalyzed cyclocarbonylation under moderate pressure and short reaction time would be advantageous for the synthesis of highly densed natural products. In this regard, we investigated the suitable reaction conditions, in particular, applicable solvents for ruthenium-catalyzed cyclocarbonylation. We initially examined solvent effect on ruthenium-catalyzed cyclocarbonylation of 3-cyclohexylhexa-4,5-dien-1-ol **1**, which was chosen as a marginally reactive allenyl alcohol.[4c] The results are shown in Table 1. Reaction of **1** with $Ru_3(CO)_{12}$ (3 mol %) in triethylamine under 5 atm of carbon monoxide at 100 °C, the same condition as those reported,[4c] afforded an inseparable mixture of *endo*-**2** and *exo*-**2** (2.1: 1) in 72% (entry 1). Based on the proposed reaction mechanism,[4b] triethylamine together with the Ru catalyst would promote the isomerization of *exo*- to *endo*-isomer. Thus, our efforts were focused on both the improvement of yield and the effective alkene isomerization. Use of *n*-butyl methyl sulfide[6] as an additive slightly improved the ratio of

(1) For some of more recent examples of 5-membered lactones, see: (a) Lei, C.; Huang, S.-X.; Chen, J.-J.; Yang, L.-B.; Xiao, W.-L.; Chang, Y.; Lu, Y.; Huang, H.; Pu, J.-X.; Sun, H.-D. *J. Nat. Prod.* **2008**, *71*, 1228–1232. (b) Jayaprakasha, G. K.; Mandadi, K. K.; Poulose, S. M.; Jadegoud, Y.; Nagana Gowda, G. A.; Patil, B. S. *Bioorg. Med. Chem.* **2008**, *16*, 5939–5951. (c) Tuchinda, P.; Kornsakulkarn, J.; Pohmakotr, M.; Kongsaeree, P.; Prabpai, S.; Yoosook, C.; Kasisit, J.; Napaswad, C.; Sophasan, S.; Reutrakul, V. *J. Nat. Prod.* **2008**, *71*, 655–663. (d) Cioffi, G.; Bader, A.; Malafronte, A.; Piaz, F. D.; Tommsai, N. D. *Phytochemistry* **2008**, *69*, 1005–1012. (e) Yang, S.-P.; Gao, Z.-B.; Wu, Y.; Hu, G.-Y.; Yue, J.-M. *Tetrahedron* **2008**, *64*, 2027–2034. (f) Tachibana, M.; Matsui, C.; Takeuchi, Y.; Suzuki, E.; Umezawa, K. *Heterocycles* **2008**, *76*, 1561–1569. For some of more recent examples of 6-membered lactones, see: (g) Sappapan, R.; Sommit, D.; Ngamrojanavanich, N.; Pengpreecha, S.; Wiyakrutta, S.; Sriubolmas, N.; Pudhom, K. *J. Nat. Prod.* **2008**, *71*, 1657–1659. (h) Pu, J.-X.; Yang, L.-M.; Xiao, W.-L.; Li, R.-T.; Lei, C.; Gao, X.-M.; Huang, S.-X.; Li, S.-H.; Zheng, Y.-T.; Huang, H.; Sun, H.-D. *Phytochemistry* **2008**, *69*, 1266–1272. (i) Iida, M.; Ooi, T.; Kito, K.; Yoshida, S.; Kanoh, K.; Shizuri, Y.; Kusumi, T. *Org. Lett.* **2008**, *10*, 845–848. (j) Marrero, J.; Benitez, J.; Rodriguez, A. D.; Zhao, H.; Raptis, R. G. *J. Nat. Prod.* **2008**, *71*, 381–389. (k) Kipassa, N. T.; Okamura, H.; Doe, M.; Morimoto, Y.; Iwagawa, T.; Nakatani, M. *Heterocycles* **2008**, *75*, 157–164. (l) Xiang, W.-S.; Wang, J.-D.; Fan, H.-M.; Wang, X.-J.; Zhang, J. *J. Antibiot.* **2008**, *61*, 27–32. For some of more recent examples of 7-membered lactones, see: (m) Miethbauer, S.; Guenther, W.; Schmidtke, K.-U.; Heiser, I.; Graefe, S.; Gitter, B.; Liebermann, B. *J. Nat. Prod.* **2008**, *71*, 1371–1375. (n) Kipassa, N. T.; Iwagawa, T.; Okamura, H.; Doe, M.; Morimoto, Y.; Nakatani, M. *Phytochemistry* **2008**, *69*, 1782–1787. (o) El, D.; Riham, S.; El, H.; Ali, M.; Ma, C.-M.; Hattori, M. *J. Nat. Prod.* **2008**, *71*, 1022–1026. (p) Jia, Z.; Lu, Y.; Liao, Z.; Chen, D. *Helv. Chim. Acta* **2007**, *90*, 1236–1243. (q) Wang, W.; Liu, J.; Han, J.; Xu, Z.; Liu, R.; Liu, P.; Wang, W.; Ma, X.; Guan, S.; Guo, D. *Planta Med.* **2006**, *72*, 450–457. (r) Pu, J.-X.; Li, R.-T.; Xiao, W.-L.; Gong, N.-B.; Huang, S.-X.; Lu, Y.; Zheng, Q.-T.; Lou, L.-G.; Sun, H.-D. *Tetrahedron* **2006**, *62*, 6073–6081.

(2) For some of more recent examples of 5-membered lactones, see: (a) Nagamitsu, T.; Takano, D.; Seki, M.; Arima, S.; Ohtawa, M.; Shiomi, K.; Harigaya, Y.; Omura, S. *Tetrahedron* **2008**, *64*, 8117–8127. (b) García, I.; Pérez, M.; Besada, P.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2008**, *49*, 1344–1347. (c) Melamed, J. Y.; Egbertson, M. S.; Varga, S.; Vacca, J. P.; Moyer, G.; Gabryelski, L.; Felock, P. J.; Stillmock, K. A.; Witmer, M. V.; Schleif, W.; Hazuda, D. J.; Leonard, Y.; Jin, L.; Ellis, J. D.; Young, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5307–5310. (d) Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931–3933. (e) Blaszczyk, K.; Koenig, H.; Paryzek, Z. *Eur. J. Org. Chem.* **2005**, *74*, 9–754. (f) Hanessian, S.; Giroux, S.; Buffat, M. *Org. Lett.* **2005**, *7*, 3989–3992. For some of more recent examples of 6-membered lactones, see: (g) Madec, D.; Mingoia, F.; Prestat, G.; Poli, G. *Synlett* **2008**, 1475–1478. (h) Hayashi, Y.; Yamaguchi, H.; Toyo shima, M.; Okado, K.; Toyo, T.; Shoji, M. *Org. Lett.* **2008**, *10*, 1405–1408. (i) Chakraborty, T. K.; Purkait, S. *Tetrahedron Lett.* **2008**, *49*, 5502–5504. (j) Enders, D.; Barbion, J. *Chem.—Eur. J.* **2008**, *14*, 2842–2849. (k) Ghosh, S.; Kumar, S. U.; Shashidhar, J. *J. Org. Chem.* **2008**, *73*, 1582–1585. (l) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2–11. For some of more recent examples of 7-membered lactones, see: (m) Volcho, K. P.; Yarovaya, O. I.; Kurbakova, S. Y.; Korchagina, D. V.; Barkhash, V. A.; Salakhutdinov, N. F. *Russ. J. Org. Chem.* **2007**, *43*, 511–517. (n) Yadav, V. K.; Agrawal, D. *Chem. Commun.* **2007**, 5232–5234. (o) Fischer, D.; Theodorakis, E. A. *Eur. J. Org. Chem.* **2007**, *419*, 3–4196. (p) Nicolaou, K. C.; Xu, H. *Chem. Commun.* **2006**, 600–602. (q) Tangirala, R. S.; Antony, S.; Agama, K.; Pommier, Y.; Anderson, B. D.; Bevins, R.; Curran, D. P. *Bioorg. Med. Chem.* **2006**, *14*, 6202–6212. (r) Briggs, T. F.; Dudley, G. B. *Tetrahedron Lett.* **2005**, *46*, 7793–7796. (s) Kobayashi, K.; Umakoshi, H.; Hayashi, K.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2004**, *33*, 1588–1589.

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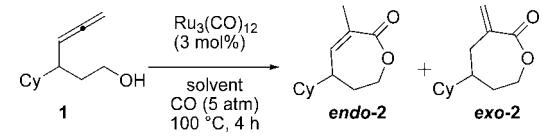
endo- and *exo*-isomer (entry 2). Several acyclic tertiary amines, dicyclohexylmethylamine, *N*,*N*,*N*′,*N*′-tetramethylethylene-diamine, and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine, provided **2** in low yields (entries 3, 5, and 6), while *N*,*N*-dimethylaminoethanol gave complex mixtures (entry 4). Among cyclic tertiary amines 1,8-diazabicyclo[5.4.0]undec-7-ene, *N*-methylpyrrolidine, *N*-methylpiperidine, and *N*-methylmorpholine, only *N*-methylpiperidine afforded **2** in 71% yield (2.6:1) (entries 7, 8, 9, and 10). To our surprise, 2,6-lutidine and 2,4,6-collidine resulted in the slight improvement of isomerization (entries 12 and 16), whereas pyridine, 2,4- and 3,5-lutidine, 2,6-dimethoxypyridine, and quinoline gave none of the desired compound (entries 11, 13, 14, 15, and 17). It should be noted that substituted pyridines, such as 2,6-lutidine and 2,4,6-collidine, are also solvents of choice, because the properties (e.g., basicity) of the aromatic amines are quite different from those of aliphatic tertiary amines, such as triethylamine and *N*-methylpiperidine.[7]

We next examined pressure effect on cyclocarbonylation of allenyl alcohol **3a**, and the results are shown in Table 2. Reaction of **3a** with 1.5 equiv of triethylamine in 1,4-dioxane under 10 atm of carbon monoxide at 100 °C, standard conditions,[4a] gave the corresponding γ-lactone **4a** in 84% (entry 1), while lowering pressure of carbon monoxide from 10 to 5 atm reduced the reactivity toward **3a** to give **4a** in 27% together with recovered starting material (entry 3). Cyclocarbonylation of **3a** in triethylamine under both 10 and 5 atm of carbon monoxide gave **4a** in 84 and 79% yields, respectively (entries 2 and 4). On the other hand, reaction of **3a** under atmospheric pressure of carbon monoxide gave **4a** in 10% yield, together with recovered starting material (entry 6). To our delight, reaction of **3a** proceeded in 2,4,6-collidine to afford **4a** without affecting the pressure of carbon monoxide (entries 5, 7, and 8).

To explore the scope of the cyclocarbonylation of allenyl alcohol in 2,4,6-collidine under an atmospheric pressure of carbon monoxide, a variety of the substituted allenyl alcohols were examined and the results are shown Tables 3 and 4. Both allenyl alcohols **3b**−**e** and **5a**−**e** afforded the corresponding five- and six-membered lactones **4b**−**e** and **6a**−**e** in 58−85% and 58−76% yields, respectively. In general, increasing the steric hindrance around alcohol moiety led to a reduction in yield (Table 3, entry 3; Table 4, entries 3 and 4).

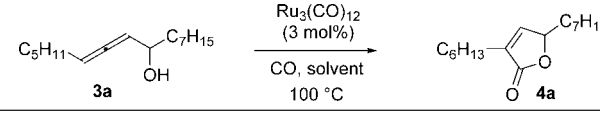
TABLE 1. Solvent Effect on Cyclocarbonylation of 1



entry	solvent	yield[a] (%)
1	NEt_3	72 (2.1:1)
2	NEt_3[b]	72 (2.6:1)
3	Cy_2NMe	43 (2.4:1)
4	$Me_2NCH_2CH_2OH$	−[c]
5	TMEDA	34 (2.1:1)
6	$MeN(CH_2CH_2NMe_2)_2$	25 (2.1:1)
7	DBU	−[d]
8	*N*-methylpyrrolidine	−[c]
9	*N*-methylpiperidine	71 (2.6:1)
10	*N*-methylmorpholine	−[c]
11	pyridine	−[d]
12	2,6-lutidine	60 (2.6:1)
13	2,4-lutidine	−[c]
14	3,5-lutidine	−[d]
15	2,6-dimethoxypyridine	−[d]
16	2,4,6-collidine	70 (3.0:1)
17	quinoline	−[c]

[a] The ratio of the *endo* to the *exo* product was determined by ^1H NMR and is given in parentheses. [b] 1.5 equiv of *n*-BuSMe was added. [c] Complex mixtures were formed. [d] Starting material was recovered.

TABLE 2. Cyclocarbonylation of Allenyl Alcohol 3a



entry	time (h)	pressure (atm)	solvent	yield (%)
1	6	10	1,4-dioxane[a]	84
2	6	10	NEt_3	84
3	4	5	1,4-dioxane[a]	27[b]
4	4	5	NEt_3	79
5	4	5	2,4,6-collidine	83
6	2	1	NEt_3	10[b]
7	2	1	2,4,6-collidine	75
8	2.5[c]	1	2,4,6-collidine	79

[a] 1.5 equiv of NEt_3 was added. [b] Starting material was recovered. [c] Slow addition of **3a** over 2 h.

Finding the utility of 2,4,6-collidine in ruthenium-catalyzed cyclocarbonylation under atmospheric pressure of carbon monoxide, we turned our attention to the application of this methodology in the synthesis of (+)-isomintlactone (**10**)[8] (Scheme 1). Alkyne **7**,[9] prepared from (+)-citronellal diethyl acetal, was converted to propargyl silane **8**, followed by one-

(3) (a) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120–122. (b) Marshall, J. A.; Snyder, W. R. *J. Org. Chem.* **1975**, *40*, 1656–1659. (c) Sugihara, T.; Coperet, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923–7924. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (e) Kindo, T.; Kodoi, K.; Mitsudo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 755–756. (f) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063–1065. (g) Constantino, M. G.; Losco, P.; Castellano, E. E. *J. Org. Chem.* **1989**, *54*, 681–683. (h) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110. (i) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707–6738. (j) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377–1396. (k) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1986**, *51*, 4323–4325.

(4) For preparation of 5- and 6-membered lactones, see: (a) Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441–443. (b) Yoneda, E.; Zhang, S.-W.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *J. Org. Chem.* **2003**, *68*, 8571–8576. For preparation of 7−8 membered lactones, see: (c) Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459–5461. For preparation of 5−6 membered lactams, see: (d) Kang, S.-K.; Kim, K.-J.; Yu, C.-M.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* **2001**, *3*, 2851–2853.

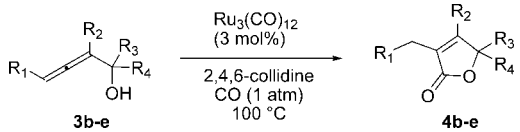
(5) Tsubuki, M.; Takahashi, K.; Sakata, K.; Honda, T. *Heterocycles* **2005**, *65*, 531–540.

(6) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771–773.

(7) K_a values for the corresponding conjugate acids of amines, triethylamine, *N*-methylpiperidine, 2,6-lutidine, and 2,4,6-collidine, are 10.6, 9.9, 6.6, 7.4, respectively. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(8) For a review on the synthesis of mintlactone and isomintlactone, see: (a) Ferraz, H. M. C.; Longo, L. S., Jr.; Grazini, M. V. A. *Synthesis* **2002**, 2155–2164. (b) Bates, R. W.; Sridhar, S. *J. Org. Chem.* **2008**, *73*, 8104–8105. (c) Pandey, R. K.; Upadhyay, R. K.; Shinde, S. S.; Kumar, P. *Synth. Commun.* **2004**, *13*, 2323–2329. (d) Ferraz, H. M. C.; Gragini, M. V. A.; Ribeiro, C. M. R.; Brocksom, U.; Brocksom, T. J. *J. Org. Chem.* **2000**, *65*, 2606–2607. (e) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Synlett* **1998**, 655–657. (f) Tanyeli, C.; Cahskan, Z.; Demir, A. S. *Synth. Commun.* **1997**, *27*, 3471–3476. (g) Lohray, B. B.; Nandana, E.; Bhushan, V. *Indian J. Chem., Sect. B* **1997**, *36*, 226–231. (h) Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron* **1993**, *49*, 6429–6436. (i) Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Gazz. Chim. Ital.* **1995**, *125*, 223–231. (j) Carda, M.; Macro, J. A. *Tetrahedron* **1992**, *48*, 9789–9800. (k) Shishido, K.; Irie, O.; Shibuya, M. *Tetrahedron Lett.* **1992**, *33*, 4589–4592. (l) Cory, R. M.; Ritchie, B. M.; Shrier, A. M. *Tetrahedron Lett.* **1990**, *31*, 6789–6792. (m) Fujita, T.; Watanabe, S.; Miharu, K.; Itoh, K.; Sugahara, K. *J. Chem. Tech. Biotech. Chem. Tech.* **1985**, *35*, 57–62. (n) Hirsch, J. A.; Estmann, R. H. *J. Org. Chem.* **1967**, *32*, 2915–2916. (o) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Schenck, G. O.; Schule-Elte, K.-H. *Tetrahedron* **1967**, *23*, 2583–2599.

TABLE 3. Substrate Scope of PhF_5CO_2H (9) in BV Reaction to Synthesis of Five-Membered Lactones 4b−e



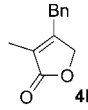
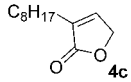
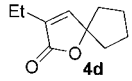
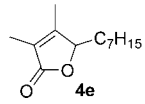
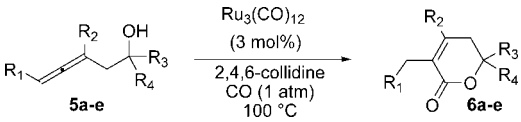
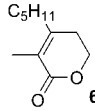
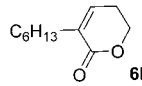
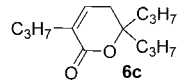
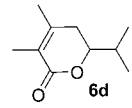
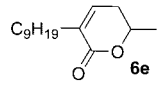
entry	allenyl alcohol	time (h)	product	yield (%)
1	**3b**; R_1=R_3=R_4=H, R_2=Bn	4	 **4b**	78
2	**3c**; R_2=R_3=R_4=H, R_1=C_7H_{15}	3	 **4c**	85
3	**3d**; R_1=CH_3, R_2=H, R_3+R_4= $(CH_2)_4$	7	 **4d**	58
4	**3e**; R_1=R_4=H, R_2=CH_3, R_3=C_7H_{15}	3	 **4e**	72

TABLE 4. Synthesis of Six-Membered Lactones 6a−e

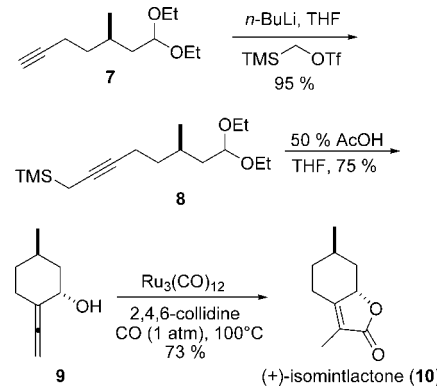


entry	allenyl alcohol	time (h)	product	yield (%)
1	**5a**; R_1=R_3=R_4=H, R_2=C_5H_{11}	5	 **6a**	73
2	**5b**; R_2=R_3=R_4=H, R_1=C_5H_{11}	3	 **6b**	76
3	**5c**; R_1=C_2H_5, R_2=H, R_3=R_4=C_3H_7	2	 **6c**	59
4	**5d**; R_1=R_4=H, R_2=CH_3, R_3=$CH(CH_3)_2$	2	 **6d**	58
5	**5e**; R_2=R_4=H, R_3=CH_3, R_1=C_8H_{17}	2	 **6e**	73

pot deacetalization−cyclization[10] gave the key allenyl alcohol **9** together with a trace of the *cis* diastereoisomer. Finally, allenyl alcohol **9** was subjected to the cyclocarbonylation reaction to furnish (+)-isomintlactone (**10**) in 73% yield, whose spectral data including the optical rotation are identical with those reported.[8h] Very recently, a synthesis of (−)-mintlactone has been accomplished using ruthenium-catalyzed cyclocarbonylation of allenyl alcohol under 7 atm of carbon monoxide by Bates et al.[8b] Since most syntheses of isomintlactone are associated with a considerable amount of either epimeric mintlactone[8d,g,h,l,m] or isomeric *exo*-α-methlene-γ-lactone,[8i,j] our synthesis would be a facile and highly stereoselective isomintlactone synthesis.

In summary, we have found a practical ruthenium-catalyzed cyclocarbonylation utilizing 2,4,6-collidine. This methodology was successfully applied for synthesis of (+)-isomintlactone.

SCHEME 1. Synthesis of (+)-Isomintlactone



Efforts to explore further applications are currently in progress in our laboratory.

Experimental Section

General Remarks. Reagents were purchased from commercial sources. 2,4,6-Collidine was used without further purification. $Ru_3(CO)_{12}$ was recrystallized from hexane before use. Allenyl alcohols **1**,[4c] **3a**,[11] **3b**,[12] **3c**,[13] **3d**,[14] **3e**,[15] **5a**,[17] **5b**,[18] **5d**,[19] **5e**[20] were prepared according to the reported method. Allenyl alcohol **5c** was prepared based on the reported method.[19] The following compounds are known and the spectra data are in accord with the literature data; **2**,[4c] **4b**.[16]

General Procedure for Ruthenium-Catalyzed Cyclocarbonylation. 5-Heptyl-3-hexylfuran-2(5*H*)-one 4a. To allenyl alcohol **3a** (100.6 mg, 0.42 mmol) in 2,4,6-collidine (6.3 mL) was added $Ru_3(CO)_{12}$ (8.1 mg, 0.01 mmol) in a 20 mL, two-necked, creased flask. The flask was flushed with 1 atm of CO. After the reaction was stirred for 2 h at 100 °C, the CO was released. The reaction mixture was poured into brine and extracted with AcOEt. The organic layer was washed with saturated aqueous $KHSO_4$ solution, brine, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was dried over Na_2SO_4 and removed in vacuo. The residue was purified by column chromatography on silica gel using hexane−AcOEt (97.5:2.5, v/v) as the eluent to give 2-furanone **4a** (84.1 mg, 74.8%) as a pale yellow oil: IR ν_{max} 1760, 2860, 2930 and 2960 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (6H, br s), 1.20−1.80 (20H, m), 2.27 (2H, t, J = 7.3 Hz), 4.89 (1H, dt, J = 1.5 and 5.4 Hz), 7.00 (1H, d, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.0 (2), 22.4, 22.5, 24.9, 25.2, 27.3, 28.8, 29.0, 29.3,

(9) Preparation of racemic alkyne **7** was reported by Hoffmann et al. Hoffmann, R. W.; Sander, T. *Liebigs Ann. Chem.* **1993**, *118*, 5–1191. We prepared chiral **7** from (+)-citronellal diethyl acetal by ozonolysis (O_3, $NaHCO_3$, $MeOH/CHCl_3$, 99%) followed by alkynation (Bestmann−Ohira reagent, K_2CO_3, MeOH, 84%) of the corresponding aldehyde in 83% overall yield. $[\alpha]^{24}_D$ +2.7 (*c* 1.0, $CHCl_3$).

(10) Clive, D. L. J.; Maarten, X. H.; Postema, H. D.; Mashimbye, M. J. *J. Org. Chem.* **1999**, *64*, 4397–4410.

(11) Horvath, A.; Baeckvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120–8126.

(12) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837–2843.

(13) Keck, G. E.; Webb, R. R., II. *Tetrahedron Lett.* **1982**, *23*, 3051–3054.

(14) Trost, B. M.; Jonasson, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2063–2066.

(15) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526–8535.

(16) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972–6975.

(17) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466–12476.

(18) Lathbury, D. C.; Shaw, R. W.; Bates, P. A.; Hursthouse, M. B.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2415–2424.

(19) Pornet, J.; Randrianoelina, B.; Miginiac, L. *J. Organomet. Chem.* **1979**, *174*, 15–26.

(20) Huynh, C.; Linstrumelle, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1133–1134.

31.4, 31.6, 33.5, 81.2, 134.4, 147.8, 173.9; MS (EI) 266 (M^+); HRMS (EI) calcd for $C_{17}H_{30}O_2$ 266.2246, found 266.2239.

Synthesis of (+)-Isomintlactone (10). [(6*R*)-8,8-Diethoxy-6-methyloct-2-yn-1-yl](trimethyl)silane 8. To a solution of alkyne **7**[9] (99.4 mg, 0.50 mmol) in THF (2 mL) was added dropwise *n*-BuLi (1.59 M in hexane, 0.44 mL, 0.70 mmol) at 0 °C under Ar. After the mixture was stirred for 0.25 h at 0 °C, a solution of $TMSCH_2OTf$ (185.1 mg, 0.75 mmol) in THF (0.5 mL) was added at 0 °C. After the reaction mixture was warmed to room temperature, it was stirred for 1.3 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine. The solvent was dried over Na_2SO_4 and removed in vacuo. The residue was purified by column chromatography on silica gel using hexane−AcOEt (95:5, v/v) as the eluent to give silane **8** (135.4 mg, 95.0%) as a oil: $[\alpha]^{31}_D$ +1.9 (*c* 1.0, $CHCl_3$); IR ν_{max} 850, 1065 and 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (9H, s), 0.88 (3H, d, J = 6.9 Hz), 1.15 (3H, t, J = 7.1 Hz), 1.16 (3H, t, J = 7.1 Hz), 1.20−1.79 (5H, m), 1.36 (3H, t, J = 2.8 Hz), 2.05−2.23 (2H, m), 3.39−3.66 (4H, m), 4.55 (1H, t, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ −2.2 (2), 6.9, 15.3 (2), 16.4, 19.2, 28.3, 36.8, 40.3, 60.2, 61.0, 77.2, 78.6, 101.4; MS (CI) 285 (M + 1); HRMS (EI) calcd for $C_{16}H_{32}O_2Si$ 284.2172, found 284.2163.

(5*R*)-2-Ethylidene-5-methylcyclohexanol (9). To the solution of silane **8** (77.6 mg, 0.27 mmol) in THF (2 mL) was added 50% AcOH. The reaction mixture was stirred for 19 h at 50 °C. The reaction was neutralized and removed in vacuo. The residue was extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and removed in vacuo. The residue was purified by column chromatography on silica gel using hexane−AcOEt (9:1, v/v) as the eluent to give allene **9** (28.1 mg, 74.5%) as a oil: $[\alpha]^{27}_D$ +81.7 (*c* 1.0, $CHCl_3$); IR ν_{max} 840, 1460, 1960 and 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.8 Hz), 1.04−1.42 (2H, m), 1.74−2.02 (4H, m), 2.17 (1H, dt, J = 4.1 and 13.8 Hz), 2.30−2.42 (1H, m), 4.42 (1H, t, J = 3.6 Hz), 4.68 (2H, d, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 21.6, 25.7, 26.0, 34.5, 41.7, 69.2, 74.6, 103.1, 203.3; MS (EI): 139 (M + 1); HRMS (EI) calcd for $C_9H_{15}O$ 139.1123, found 139.1142.

(+)-Isomintlactone (10). To allene **9** (92.2 mg, 0.67 mmol) in 2,4,6-collidine (9.8 mL) was added $Ru_3(CO)_{12}$ (12.8 mg, 0.02 mmol) in a 20 mL, two-necked, creased flask. The flask was flushed with 1 atm of CO. After the reaction mixture was stirred for 3 h at 100 °C, the CO was released. The reaction mixture was poured into brine and extracted with AcOEt. The organic layer was washed with saturated aqueous $KHSO_4$ solution, brine, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was dried over Na_2SO_4 and removed in vacuo. The residue was purified by column chromatography on silica gel using pentane−AcOEt (9:1, v/v) as the eluent to give (+)-isomintlactone (**10**) (80.5 mg, 72.6%) as a white solid. Its NMR and MS spectra data are in agreement with those reported:[8h] mp 79−80 °C (Et_2O/pentane) (lit.[8h] mp 78−79 °C); $[\alpha]^{28}_D$ +79.7 (*c* 0.7, EtOH) [lit.[8h] $[\alpha]_D$ +79 (*c* 0.7, EtOH)].

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Supporting Information Available: Preparation and characterization data of **5c** and **7** and ^1H NMR and ^{13}C NMR spectral data for **2**, **4c**,**d**, and **6a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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