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Stereoselective construction of a quaternary carbon substituted with multifunctional groups: application to the concise synthesis of (+)-ethosuximide

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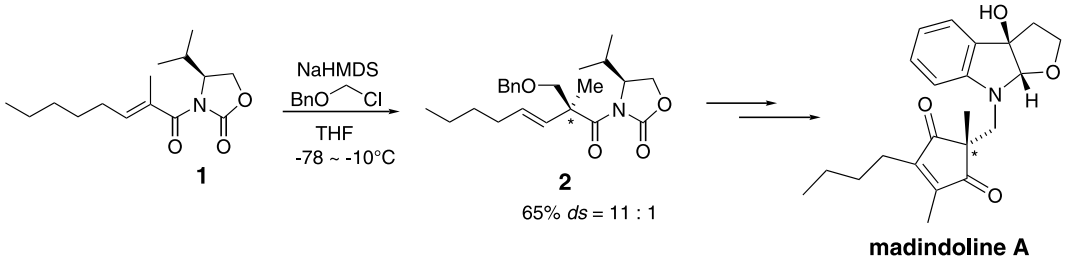
Abstract—Synthetically useful β,γ-unsaturated carbonyl compounds having a quaternary carbon at the α-position were prepared with high stereoselectivity by the reaction of a dienolate anion derived from α,β-unsaturated imide having a chiral auxiliary and electrophiles (ethyl acetate and allyl iodide as the C_2 and C_3 unit, respectively). This method was applied to a short asymmetric synthesis of (+)-ethosuximide.

During the course of our total synthesis of madindoline A,[1] stereochemical control of the quaternary chiral center in the cyclopentene moiety was achieved by developing a highly diastereo- and regioselective α-alkylation of the α,β-unsaturated chiral imide (Scheme 1). While a number of methodologies have been developed for the construction of a quaternary chiral center,[2] efficient and general methods are still required. As demonstrated by the successful total synthesis of madindoline A, the resulting β,γ-unsaturated imides are considered valuable synthetic intermediates for the synthesis of a variety of biologically significant compounds utilizing both a carbon–carbon double bond and a carboxyl group. The electrophiles employed in the previous investigation were limited to benzyloxymethyl chloride (BOMCl) or methoxymethyl chloride (MOMCl) aiming at the madindoline synthesis, and the stereoselectivities were moderate, ranging from 6:1 to 11:1.[1] In order to expand the scope of this methodology, it seemed necessary to demonstrate the reaction of α,β-unsaturated chiral imide with other alkyl halides. In this paper we wish to describe the alkylation with iodoacetate and allyl iodide as the C_2 and C_3 units, respectively.

Our method to construct a quaternary chiral center is shown in Scheme 2. The γ-proton of α,β-unsaturated imide **1** was deprotonated with sodium hexamethyldisilazide, and the resulting dienolate was reacted with electrophiles at the α-position in a regio- and stereoselective manner.[1,3,4]

At first, alkylation with allyl iodide was examined (Table 1).[5] The alkylation proceeded regioselectively at



Scheme 1.

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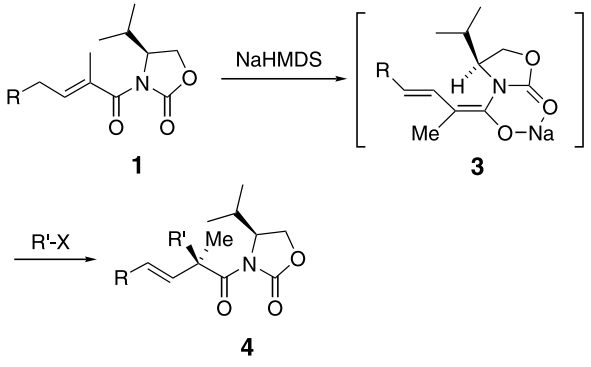
the α-position, and the corresponding α-allyl-β,γ-unsaturated imides were obtained with high stereoselectivities. In the case of β,γ-disubstituted products (entries 4–6), only *E*-isomers were obtained. The β,γ-disubstituted olefins (entries 5 and 6) were obtained in higher yield than the bis(*exo*-olefin) products (entries 2 and 3).

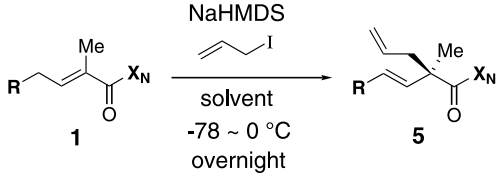
The stereochemistry of the newly formed quaternary center was determined as shown in Scheme 3. Thus, **5a** was transformed into the known 2-ethyl-2-methylpentanoic acid **6**[6] by hydrolysis and subsequent hydrogenation. The absolute configuration of **5b** was confirmed to be *R* by correlating to the caboxyacetal **7** ($[\alpha]_D^{26}$ +24.6°) by a four-step sequence: (i) iodolactonization of unsaturated imide; (ii) ozonolysis of the remaining carbon–carbon double bond; (iii) acetalization of the resulting aldehyde; and (iv) reductive elimination of iodolactone. The carboxyacetal **7** was found to be identical with the carboxyacetal **7** ($[\alpha]_D^{26}$ +23.2°) derived from the stereochemically established **5a** in a similar sequence of reactions.

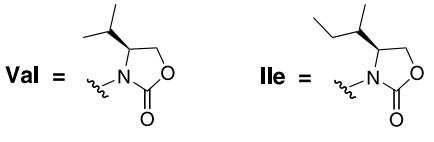
Next, we attempted the alkylation with ethyl iodoacetate as a C_2 unit (Table 2). The reaction proceeded smoothly to afford a chiral quaternary center with excellent stereoselectivity. Stereochemistry was tentatively assigned as shown in analogy to the case of the reaction with allyl iodide. In order to demonstrate the usefulness of this methodology as well as to confirm the stereochemistry, the product shown in entry 1 was converted to (+)-ethosuximide,[7,8] commonly used in the treatment of petit mal epilepsy. (Scheme 4). Heating a mixture of imide **8** and urea without a solvent gave cyclic imide **9** which was subjected to hydrogenation in the presence of a Pt catalyst. Thus, only three-step synthesis of (+)-ethosuximide from **1** was accomplished.



Scheme 2.

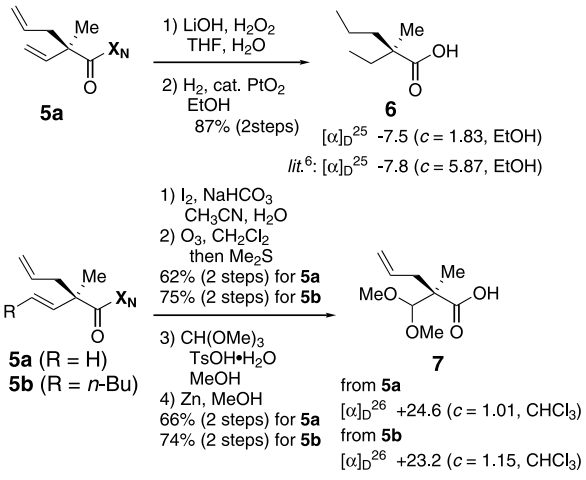
Table 1. Alkylation with allyliodide





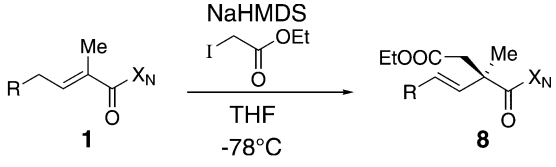
Entry	R	X_N	Solvent	Yield (%)	Selectivity[a]
1	H	**Val**	Toluene	27	42:1
2	H	**Val**	THF	61	27:1
3	H	**Ile**	THF	62	19:1
4	Bu	**Val**	Toluene	30	29:1
5	Bu	**Val**	THF	76	22:1
6	Bu	**Ile**	THF	71	29:1

[a] Determined by HPLC.



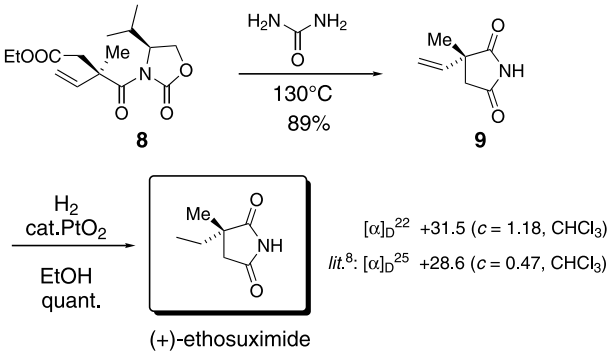
Scheme 3.

Table 2. Alkylation with ICH_2CO_2Et



Entry	R	X_N	Yield (%)	Selectivity[a]
1	H	**Val**	76	31:1
2	H	**Ile**	67	38:1
3	Bu	**Ile**	85	>50:1

[a] Determined by ^1H NMR.



Scheme 4.

In conclusion, we were able to develop a concise and highly stereoselective method for the construction of a quaternary carbon and accomplish a short synthesis of (+)-ethosuximide. The stereochemical course of the present alkylation is the same in all cases. The present methodology can provide a useful synthetic intermediate having a quaternary chiral carbon substituted with multifunctional groups (vinyl, allyl, and acetate). Further application of this methodology toward natural products is now in progress.

Acknowledgements

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References

1. (a) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett*. **2000**, *41*, 6429–6433; (b) Hosokawa, S.; Kobayashi, S. *J. Synth. Org. Chem. Jpn*. **2001**, *59*, 1103–1108.
2. For excellent reviews covering most methods for the asymmetric creation of quaternary carbon centers: (a) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037–2066; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 388–401.
3. For alkylation affording a chiral tertiary carbon: (a) Evans, D. A.; Ennis, M. D.; Mathre D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737–1738; (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett*. **1980**, *21*, 4233–4236.
4. For stereoselective alkylation of α,β-unsaturated carboxylic acid derivatives: (a) Tomooka, K.; Nagasawa, A.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett*. **1996**, *37*, 8895–8898; (b) Tomooka, K.; Nagasawa, A.; Nakai, T. *Chem. Lett*. **1998**, 1049–1050.
5. General procedure of the alkylation with allyl iodide was as follows: To a solution of α,β-unsaturated chiral imide (99.0 mg, 370 μmol) in THF (4.0 mL) was dropwise added a solution of NaHMDS (1.0 M in THF, 0.75 mL, 750 μmol) at −78°C. After stirring for 90 min at −78°C, allyl iodide (380 mL, 4.10 mmol) was dropwise added to the mixture, which was stirred at −50°C for 6 h. The reaction mixture was quenched with satd NH_4Cl, and was extracted with AcOEt (×3). The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation and purification by SiO_2 column chromatography (hexane:ethyl acetate = 10: 1) gave **5b** 86.5 mg (76%) as colorless syrup. **5b**: $R_f = 0.76$ (hexane:AcOEt = 2:1); $[\alpha]_D^{24}$ +62.2 (*c* 1.65, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.87 (3H, t, $J = 6.4$ Hz), 0.88 (3H, d, $J = 6.7$ Hz), 0.91 (3H, d, $J = 7.0$ Hz) 1.24–1.34 (4H, m), 1.36 (3H, s), 1.97–2.03 (2H, m), 2.26–2.37 (1H, m), 2.52 (1H, dd, $J = 13.7$, 7.1 Hz), 2.97 (1H, dd, $J = 13.7$, 7.6 Hz), 4.16 (1H, dd, $J = 8.9$, 2.8 Hz), 4.21 (1H, dt, $J = 8.3$, 3.4 Hz), 5.06 (1H, d, $J = 10.1$ Hz), 5.10 (1H, d, $J = 17.1$ Hz), 5.31 (1H, dt, $J = 15.9$, 7.1 Hz), 5.69–5.79 (1H, m), 5.81 (1H, dt, $J = 15.9$, 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 13.8, 14.7, 18.1, 22.1, 24.4, 28.5, 31.4, 32.2, 42.7, 49.4, 60.1, 62.9, 118.2, 129.6, 133.6, 134.0, 152.1, 175.8. IR (neat) 3077, 2961, 2929, 2873, 1787, 1685, 1639, 1465, 1384, 1362, 1299, 1230, 1200, 1148, 1092, 1062, 992, 996, 917 cm^{-1}
   The alkylation with ethyl iodoacetate was carried out in a similar manner except for the reaction temperature.
6. Kogen, H.; Tishihama, S.; Koga, T.; Kitazawa, E.; Serizawa, N.; Hamano, K. *Eur. Pat. Appl*. **1994**, 154.
7. (a) Sorel, L. *Acta Neurol. Psychiat. Belg*. **1960**, *60*, 551–559; (b) Hirai, T.; Ando, N.; Naoi, T.; Inoue, R.; Watanabe, H. *Seishin Igaku* **1965**, *7*, 142.
8. (a) Knabe, J.; Koch, W. *Arch. Pharm*. **1972**, *305*, 757–765; (b) Knabe, J.; Plisch, J. *Tetrahedron Lett*. **1973**, *14*, 745–746; (c) Nishide, K.; Katoh, T.; Imazato, H.; Node, M. *Heterocycles* **1998**, *47*, 839–845; (d) Katoh, T.; Nishide, K.; Node, M.; Ogura, H. *Heterocycles* **1999**, *48*, 833–841.