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LETTERS

A general method for the highly diastereoselective, kinetically controlled alkylation of (+)-nopinone

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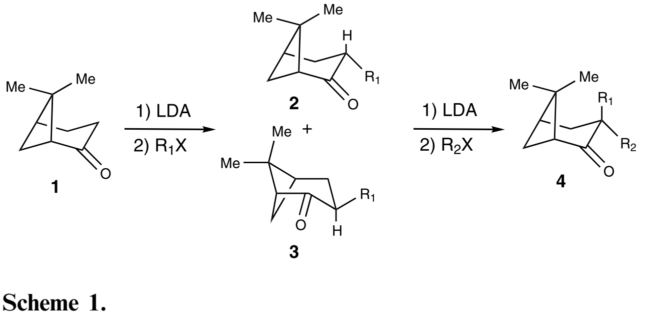
Abstract—A general method for the monoalkylation of (+)-nopinone was developed for a variety of carbon and heteroatom electrophiles to afford the kinetically controlled product **2** with high diastereoselectivity (98% d.e.) and excellent yield (75–90%).

Although (+)-nopinone **1**[1] is readily available from β-pinene, its use as a chiral scaffold in natural products synthesis is limited. This may be due in part because the monoalkylation of the enolate of (+)-nopinone with alkyl halides affords a mixture of diastereomers **2** and **3**, usually favoring the thermodynamically preferred product **3** (Scheme 1).[2] In contrast, alkylation of the subsequent mixture of diastereomers with a different electrophile affords the dialkylated product **4** as a single diastereomer. Products such as **4** have been applied to several natural products syntheses;[3] however, due to the lack of a general diastereoselective method to access **2**, the 3-monosubstituted nopinones have remained unused. We herein wish to report a highly diastereoselective monoalkylation of (+)-nopinone with a variety of carbon and heteroatom electrophiles to afford the kinetically preferred product **2** with no epimerization to its thermodynamically favored counterpart **3**.

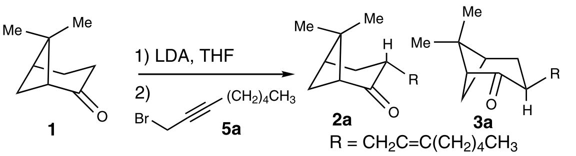


Scheme 1.

Our initial efforts were focused on the alkylation of the enolate of (+)-nopinone, generated from lithium diisopropylamide (LDA), with propargyl bromide **5a**. We quickly discovered that the temperature of the reaction had a dramatic effect on the yield and selectivity of the alkylation (Table 1). At higher temperatures, the yields were respectable, but the diastereoselectivity was poor (72:28), favoring the kinetically preferred product **2a**.[4] Conversely, as the temperature was decreased, diastereomeric ratios as high as 99:1 favoring **2a** were observed, but the yields dropped to as low as 15%.

These results indicate a highly diastereoselective, kinetically controlled alkylation to afford **2a** at low temperature, which is competitive with epimerization to the

Table 1. Nopinone alkylation: dependence of diastereoselectivity and yield on temperature[a]



Temperature (°C)	Conversion (%)[b]	**2a**:**3a**[c]
0	85	72:28
−25	68	90:10
−35	50	96:4
−45	30	99:1
−55	15	99:1

[a] All reactions were carried out in THF (1.2 M in substrate) using 1.05 equiv. LDA and 1.05 equiv. **5a**.

[b] Conversion was determined 1.5 h after addition of **5a** (HPLC).

[c] Diastereoselectivity was determined by HPLC.

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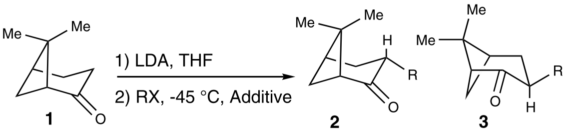
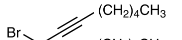
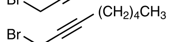
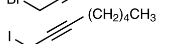
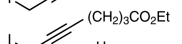
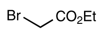
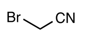
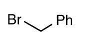
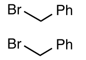
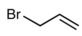
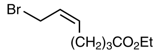
thermodynamically favored product **3a** at higher temperatures. In order to access **2a** in good yield, the reactivity of the enolate or the electrophile must be increased such that the alkylation would occur at −45°C. When the alkylation with **5a** was performed with 1 equivalent of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at −45°C, a high yield and high diastereoselectivity were observed (90% yield, 99:1 **2a**:**3a**).[5] Alternatively, when the more reactive propargyl iodide **5b** (Table 2) was used in the alkylation in the absence of DMPU, a similarly high yield and diastereoselectivity were observed (90% yield, 99:1 **2a**:**3a**). In every case, the reaction was quenched at low temperature (see general procedure) in order to avoid epimerization to the thermodynamically favored product.[6]

With optimized reaction conditions in hand, a variety of carbon electrophiles were investigated to demonstrate scope and practicality (Table 2). Many of the electrophiles investigated displayed similar yields and selectivities to that of the original propargyl halide system; however, more reactive electrophiles **5e**,**f** required lower reaction temperatures to afford high diastereoselectivities. Less reactive electrophiles such as **5g**–**i** afforded good diastereoselectivities but only moderate yields (30%) of the alkylated adducts even with DMPU as an additive. In order to obtain good yields for these substrates, it was necessary to premix the electrophile with NaI in DMPU/THF to generate the iodide in situ.

Table 2. Diastereoselective nopinone alkylation with carbon electrophiles[a]



RX		Additive	% yield[b]	**2** : **3**[c]
	**5a**	none	30	98:2 (**2a**:**3a**)
	**5a**	1 equiv DMPU	89	99:1 (**2a**:**3a**)
	**5b**	none	90	99:1 (**2b**:**3b**)
	**5c**	none	90	99:1 (**2c**:**3c**)
	**5d**	1 equiv DMPU	85	99:1 (**2d**:**3d**)
	**5e**	1 equiv DMPU[e]	95	99:1 (**2e**:**3e**)
	**5f**	1 equiv DMPU[f]	95	99:1 (**2f**:**3f**)
	**5g**	none	15	98:2 (**2g**:**3g**)
	**5g**	1 equiv NaI, DMPU	78	99:1 (**2g**:**3g**)
	**5h**	1 equiv NaI, DMPU	82	99:1 (**2h**:**3h**)[d]
	**5i**	1 equiv NaI, DMPU	82	99:1 (**2i**:**3i**)
CH_3I	**5j**	1 equiv DMPU[f]	75	99:1 (**2j**:**3j**)[d]

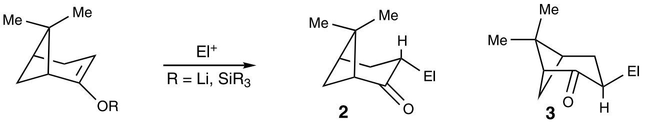
[a] All reactions were carried out in THF (1.2M in substrate) using 1.05 equiv LDA and 1.05 equiv RX. [b] Assay yield of the reaction was determined by HPLC. [c] Diastereoselectivity was determined by HPLC and stereochemistry was determined by 1H-NMR. [d] Diastereoselectivity was determined by GC. [e] The reaction was run at -50 °C. [f] The reaction was run at -78 °C.

Having demonstrated the highly diastereoselective alkylation of the enolate of (+)-nopinone with a variety of carbon electrophiles, we sought to apply this method to some heteroatom electrophiles. Sulfenylation of the enolate of (+)-nopinone at −78°C afforded good diastereoselectivity (96:4, **2k**:**3k**) and good yield (80%) of the kinetically preferred diastereomer **2k** (Table 3).[7] The bromination of the lithium enolate of (+)-nopinone with *N*-bromosuccinimide (NBS) was quite unselective, even at −78°C (42% yield, 75:25, **2l**:**3l**). In contrast, the bromination of the enolsilane of (+)-nopinone with NBS afforded the kinetically favored diastereomer **2l** in excellent yield and high diastereoselectivity (98:2, **2l**:**3l** at −78°C).[8] In fact, the diastereoselectivity was still high when run at room temperature (94:6, **2l**:**3l**).

The high diastereoselectivity of the bromination of the enolsilane of (+)-nopinone at elevated temperatures encouraged us to investigate the oxidation of the silyl enol ether of (+)-nopinone, a reaction that is typically run at 0°C.[9] Following the literature procedure (*m*CPBA/NaHCO$_3$), the oxidation afforded clean conversion to hydroxyketone **2m** with high diastereoselectivity (98:2, **2m**:**3m**) and good yield (60%).[10] This method was also applied to the azidation of the enolsilane of (+)-nopinone via the oxidative addition of azide anion using ceric ammonium nitrate.[11] Treatment of the TIPS enol ether of (+)-nopinone under azidation conditions published in the literature afforded the α-azidoketone **2n** with high diastereoselectivity (97:3, **2n**:**3n**) and good yield (73%).

In conclusion, a general procedure for the highly diastereoselective alkylation of the enolate of (+)-nopinone has been developed to afford the kinetically

Table 3. Diastereoselective nopinone sulfenylation, bromination, hydroxylation, and azidation



El+	R	Yield (%)[e]	El	**2**:**3**[f]
p-TolSSO$_2$*p*-Tol	Li[a]	80	S*p*-Tol	96:4 (**2k**:**3k**)
NBS	TMS[b]	80	Br	98:2 (**2l**:**3l**)
*m*CPBA/NaHCO$_3$	TMS[c]	60	OH	98:2 (**2m**:**3m**)
NaN$_3$/CAN	TIPS[d]	73	N$_3$	97:3 (**2n**:**3n**)

[a] Reaction was carried out in THF (1.2 M in substrate) using 1.05 equiv. LDA and 1.05 equiv. thiosulfonate at −78°C for 1.5 h.

[b] Trimethylsilyl enol ether was formed in situ (1.05 equiv. LDA, 1.05 equiv. TMSCl) before addition to a THF solution of the heteroatom electrophile (1.05 equiv., 1.25 M) at −78°C.

[c] Trimethylsilyl enol ether was isolated prior to addition to a solution of *m*CPBA (1.05 equiv.) and NaHCO$_3$ (4.4 equiv.) in CH$_2$Cl$_2$ at 0°C.

[d] Triisopropylsilyl enol ether was isolated prior to mixing with NaN$_3$ (4.5 equiv.) in MeCN followed by addition of CAN (3 equiv., 0.4 M in MeCN) at −20°C.

[e] Assay yield was determined by HPLC.

[f] Diastereoselectivity was determined by GC.

controlled product. This versatile method affords no epimerization to the thermodynamically favored product, is applicable to wide range of carbon and heteroatom electrophiles, and provides access to an underutilized natural product scaffold containing diverse functionality.

General experimental procedure: To a solution of diisopropylamine (0.8 M in THF; 10 mL, 8 mmol) was added *n*-BuLi (2.41 M in hexane; 3.2 mL, 7.7 mmol) at −10°C under N_2 with stirring. The LDA solution was aged for 15 min before (+)-nopinone (1.0 mL, 7.24 mmol) was added dropwise with the temperature maintained between −10 and −15°C. After 10 min, the mixture was cooled to −50°C and DMPU (0.88 mL, 7.24 mmol) was added to the solution. The appropriate electrophile (7.7 mmol) was then added dropwise with the temperature strictly maintained between −47 and −45°C and stirred for 1.5 h after the addition was complete. Trifluoroacetic acid (0.86 mL, 10.9 mmol) was then added while keeping the reaction temperature lower than −45°C. Upon complete addition of TFA, the solution was allowed to warm up to −10°C after which the mixture was partitioned between 3% L-tartaric acid solution (20 mL) and EtOAc (20 mL). The layers were separated and the organic layer was evaporated under reduced pressure to yield the crude product in 80–90% assay yield and purified by flash chromatography using silica and AcOEt/Hex or MTBE/Hex as the eluent.

Acknowledgements

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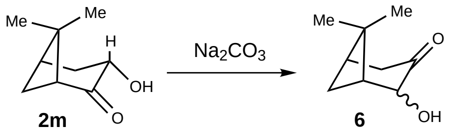
2. (a) Kato, M.; Watanabe, M.; Vogler, B.; Awen, B.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071–7076; (b) The only exception is the alkylation with methyliodide, which affords 70% isolated yield of **2** (R = Me). See: Konopelski, J. P.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2297–2301.
3. (a) Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1706–1707; (b) Inokuchi, T.; Asanuma, G.; Torii, S. *J. Org. Chem.* **1982**, *47*, 4622–4626; (c) Yanami, T.; Miyashita, M.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 607–612; (d) Van Der Gen, A.; Van Der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pay-Bas.* **1971**, *90*, 1034–1044.
4. Diastereomer **2a** (stereochemistry determined by ^{1}H NMR) was treated under thermodynamic equilibration with NaOEt in EtOH to yield **3a** (stereochemistry confirmed by ^{1}H NMR) as the major product. The diastereomeric ratio of **2a**:**3a** was determined to be 15:85 by HPLC.
5. Other additives (HMPA, TMEDA) were also investigated but none were as effective as DMPU. Alkylation is complete within 1.5 h at −45°C. Lower temperatures afforded sluggish reactions.
6. When the reaction was quenched by direct addition of aqueous acid, some epimerization to the thermodynamically favored product was always observed. In contrast, the reaction can be quenched by direct addition of trifluoroacetic acid (TFA) to the reaction solution at −45°C or by reverse quench of the reaction solution at −45°C into a 1:1 mixture of MTBE:satd NH_4Cl (aq) with no epimerization.
7. Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D. *J. Org. Chem.* **1988**, *53*, 2881–2889.
8. The bromination of (+)-nopinone has been reported albeit in lower yield and unreported diastereoselectivity. See: Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50–52 and references cited therein.
9. Jauch, J. *Tetrahedron* **1994**, *50*, 12903–12912 and references cited therein.
10. The main impurity was unreacted starting material. The actual product of the oxidation is the TMS-protected hydroxyketone, which is deprotected with Na_2CO_3. If the deprotection was allowed to stir for prolonged periods of time, isomerization from **2m** to **6** was observed.



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