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Unprecedented stereocontrol in the synthesis of 1,2,3-trisubstituted tetrahydro-*β*-carbolines *via* a new asymmetric Pictet—Spengler reaction towards sarpagine-type indole alkaloids

M. Toufiqur Rahman and James M. Cook*

Abstract: The asymmetric Pictet-Spengler (P-S) reaction of chiral N_b-ethynyl substituted tryptophan methyl ester derivatives (from both D- and L-tryptophan) with a simple aliphatic aldehyde, exhibited unprecedented selectivity towards either of the diastereomeric products. A simple variation of conditions could alter the outcome of the cyclization from either 100% *trans*-selective to 100% *cis*-selective originating entirely from internal asymmetric induction under mild conditions. This resulted in a highly efficient access to both 1,3-*cis*-(1,2,3-trisubstituted tetrahydro-*β*-carbolines, TH*β*Cs) and 1,3-*trans*-(1,2,3-trisubstituted TH*β*Cs). To the best of our knowledge, this type of stereocontrol has never been observed from tryptophan methyl ester derivatives (either D or L) in accessing either 1,3-disubstituted or 1,2,3-trisubstituted TH*β*Cs. By exploiting this very useful ambidextrous-diastereoselectivity, we have set the crucial C-3 and C-5 stereocenters of C-19 methyl substituted sarpagine-macroline-ajmaline alkaloids beginning with the DNA-encoded and cheaper L-(-)-tryptophan, as well as optionally from commercially available D-(+)-tryptophan.

The Pictet-Spengler (P-S) reaction of tryptophan derivatives with an aldehyde other than formaldehyde results in two diastereomeric TH*β*Cs (at C-1 and C-3 of the TH*β*C, see Scheme 1). The TH*β*C moiety deserves special attention in its own right as it is at the core of numerous bioactive alkaloids, as well as medicinally important synthetic analogs. As a consequence numerous studies accessing this moiety by various strategies have been undertaken.[1] Almost all useful compounds containing the TH*β*C core (both natural and synthetic) bear a stereocenter at C-1. On the other hand, in the vast majority of the sarpagine/ajmaline-type alkaloids, there is *cis*-1,3-disubstitution in the TH*β*C core (*cis*-3,5 of alkaloids in Figure 1). As a result, the diastereoselectivity of the P-S reaction to access the 1,3-*cis*-TH*β*C core is of special importance. Numerous attempts have been made to gain control in the selectivity in this process by varying the temperature, solvent, chiral catalysts, chiral reactive partners (including chiral aldehyde equivalents), and different tryptophan alkyl esters, etc.[1a, 2]

The asymmetric P-S reaction has undergone elegant advances by Jacobsen,[3] Nakagawa,[4] Bailey,[5] Misicka,[6] Hiemstra,[7] Van Maarseveen,[7] List,[8] and many others.[8] *Cis*-Selectivity in the asymmetric P-S reaction has been reported in the preparation of 1,3-disubstituted TH*β*Cs.[5b, 5c, 6a, 8g, 8h, 9] In the case of 1,3-disubstituted TH*β*C, Bailey, Sato, Misicka, and Shi have made notable advances in devising a *cis*-selective P-S reaction to gain access to the *cis*-1,3-disubstituted TH*β*C system (see SI, Scheme S-1). These strategies are logical in a chemical sense because of their promise to access the C-3 stereochemistry of indole alkaloids, starting from L-tryptophan. The requirement of pi-systems either at C-1 or C-3 however, is not desirable since very often these esters or aldehyde equivalents are surprisingly hard to prepare and require special processes for removing them. Moreover, often the products are not useful toward the synthesis of alkaloids which would require complex transformations. To the best of our knowledge, completely *cis*-selectivity in the P-S reaction with tryptophan methyl esters and aliphatic aldehydes have not been reported yet.

On the other hand, for 1,2,3-trisubstituted TH*β*C systems, the P-S reaction of N_b-benzylated tryptophan methyl esters (e.g., **1**) with aldehydes or acetals (e.g., **2**) is well known for complete *trans*-selectivity under thermodynamic conditions yielding 1,3-*trans*-1,2,3-trisubstituted TH*β*Cs **3** (Scheme 1, entry 1).[1a] This robust strategy has been employed on up to 600 gram scale processes and in excellent diastereo (100% *de*) and enantioselectivity (up to 98% *ee*) in excellent yield, while avoiding chromatographic purification. The syntheses of numerous indole and oxindole alkaloids with potent biological activity have utilized this *trans*-specific method.[10] Many examples of the preparation of 1,2,3-trisubstituted TH*β*Cs are present in the literature *via* thermodynamic control to give mostly (if not exclusively), *trans*-1,3-disubstitution.[8e, 8i, 8k] To the best of our knowledge, *cis*-specificity in preparing 1,2,3-trisubstituted TH*β*Cs from tryptophan alkyl esters is absent in the literature. Herein, we report unprecedented stereocontrol in *cis*- and *trans*-selectivity in accessing 1,2,3-trisubstituted TH*β*Cs from chiral N_b-ethynyl substituted tryptophan derivatives **4** with simple aliphatic aldehydes **5** to furnish either completely the *cis*-diastereomer **6** or the *trans*-isomer **7**, controlled by simple changes in reaction conditions (Scheme 1, entry 2). This strategy will greatly improve the approach towards the total synthesis of either the (+) or (-) enantiomer of a group of more than thirty sarpagine/macroline-/ajmaline indole alkaloids. Depicted in Figure 1 are a few representative examples (**8**-**13**)[11] from this group of bioactive alkaloids (for more examples see the SI, Figure S-1). Furthermore, the complete *cis*-selectivity would permit the synthesis to begin with the natural and cheaper L-tryptophan methyl ester instead of D-tryptophan methyl ester which has been used previously. In this version of the P-S reaction, it is the ability to prepare both the (+) or (-) enantiomer of these indole alkaloids from either D-(+)-tryptophan or L-(-)-tryptophan is of significance and illustrated here for the first time.

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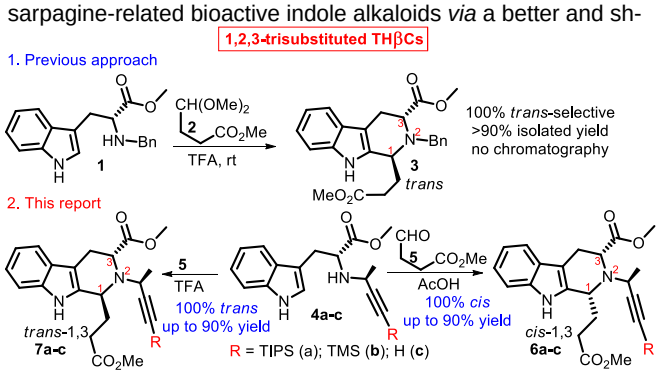
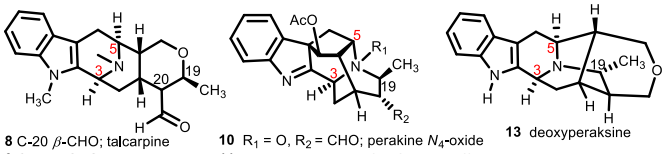
Recently, we published the total synthesis of a number of sarpagine-related bioactive indole alkaloids *via* a better and sh-



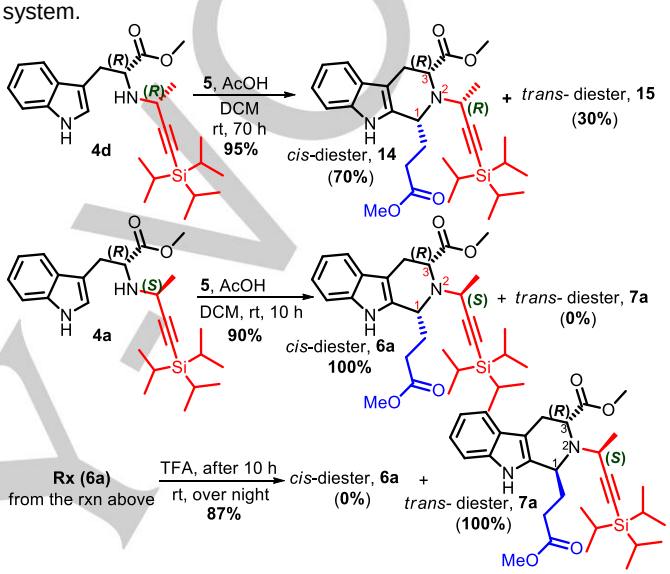
Scheme 1. Access to 1,3-disubstituted and 1,2,3-trisubstituted THβCs via the asymmetric Pictet-Spengler reaction



8 C-20 β-CHO; talcarpine
9 C-20 α-CHO; *N*4-methyl,*N*4-21-secotalpinine
10 R_1 = O, R_2 = CHO; perakine N_4-oxide
11 R_1 = no atom, R_2 = CH_2OH; raucaffrinoline
12 R_1 = O, R_2 = CH_2OH; raucaffrinoline N_4-oxide
13 deoxyperaksine

Figure 1. representative examples of C-19 methyl substituted sarpagine/ajmaline indole alkaloids **8-13**

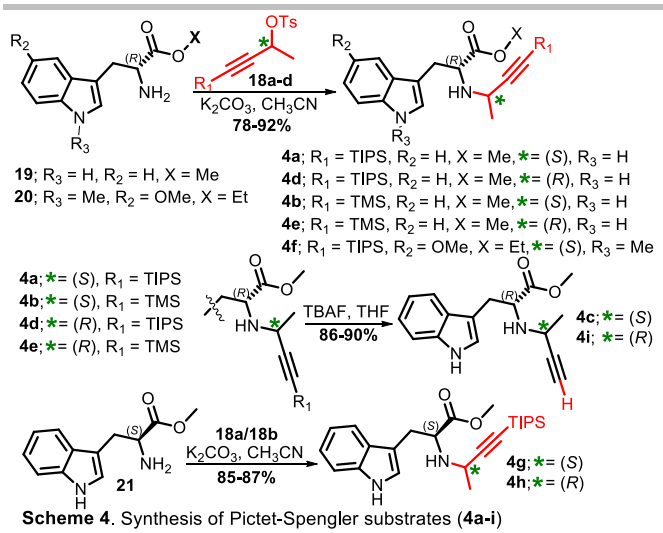
orter route for accessing the core-tetracyclic intermediates employing an improved P-S strategy.[12] One of the principal goals of that study was to gain quicker access to the key-intermediates, improving the previous strategy, and developing a shorter route to the tetracyclic-core required for an important group of more than thirty[10c, 13] alkaloids. Several interesting observations were noted in the P-S/Dieckmann protocol.[12a] When D-tryptophan methyl ester derivative with an N_b-ethynyl substituent bearing a methyl group with the (*S*) stereochemistry (**4a**) reacted with acetal **2** in acidic media (TFA in DCM), excellent diastereoselectivity (>95:5) towards the *trans*-diester (**7a**) was observed (not shown here).[12a] On the other hand, when the reaction of the tryptophan methyl ester derivative with the (*R*)-methyl substituent (**4d**) was stirred under the same conditions, this resulted in a complex reaction mixture. Afterwards, it was discovered milder reaction conditions using the aldehyde **5** and acetic acid instead of the acetal **2** and trifluoroacetic acid altered the chemistry. The asymmetric P-S reaction of the amine **4d** with aldehyde **5** proceeded smoothly under the modified and milder conditions to provide a 70 to 30 mixture of *cis* to *trans*-diastereomers in 95% combined isolated yield (Scheme 2).[12a] The excellent overall yield and diastereoselectivity towards the *cis*-diester captured our attention. A further investigation of this reaction, in order to find conditions for better selectivity became the focus. As a step toward this, the same conditions were applied to N_b-(*S*)-methyl-ethynyl substituted tryptophan derivative (**4a**). To our surprise, the reaction was complete in 10 hours and provided the *cis*-diester **6a** with 100% cis-diastereoselectivity. The addition of 3 equivalents of TFA after the initial P-S reaction (at 10 hours), converted the *cis*-diester **6a** completely into the corresponding *trans*-diester **7a** (Scheme 2). Furthermore, addition of 4 Å molecular sieves to the reaction had, as expected, a tremendous effect on the rate. Reactions run in the presence of molecular sieves were complete in several hours instead of several days. It is felt, the amine **4a** reacts with the aldehyde **5** in the presence of AcOH to form the kinetic product (*cis*-diester, **6a**) while acetic acid is not acidic enough to facilitate cleavage of the C(1)-N(2) bond which normally provides only the *trans*-diastereomer.[14] Conversely, when the kinetic product (i.e., **6a**) was treated with TFA in DCM, the *cis*-diastereomer rearranged completely to the thermodynamic product (i.e., the *trans*-product **7a**). To the best of our knowledge, this type of selectivity in the formation of completely *cis*- or *trans*-THβC from a single tryptophan derivative has never been seen in the formation of the 1,2,3-trisubstituted THβC-system.



Scheme 2. Unprecedented stereocontrol in the asymmetric P-S reaction

Encouraged by the unprecedented outcome of the P-S reaction, it was felt of importance to investigate the underlying reason(s) for this ambidextrous-diastereoselectivity. It was obvious exploitation of complete *cis*-selectivity would permit the synthesis of sarpagine alkaloids with the cheaper and natural L-(-)-tryptophan, instead of D-(+)-tryptophan. The optically pure tosylate units (**18a-d**) required for amines **4a-i** were synthesized, as depicted in Scheme 3 (see note 16 and SI).

The synthesis of amine-substrates (**4a-i**) for the P-S reaction were performed, as shown in Scheme 4. With all the required substrates in hand, the planned reactions were performed with 1 equivalent of the amines, 1.5 equivalents of the aldehyde, 3 equivalents of acetic acid, 200 mg 4 Å MS (per mmol of amines). The reactions were performed parallel at 0 °C and at rt. The outcome of these experiments are listed in Table 1. These reaction processes gave excellent overall isolated yields (up to 95%) with selectivity towards *cis*-diesters. All the *cis*- and *trans*-diester products were easily separable by silica gel column chromatography except for (entry 6) where both of them had the same R_f in several solvent systems. Interestingly, some clear patterns emerged. For example, when the carbon atoms **a** and **b** had the same configurations (*S*,*S*) or (*R*,*R*) (Table 1, entries 2, 4, 6, and 8), reactions were up to 82% *cis*-selective. The *cis*-selectivity improved at lower temperature (e.g., Table 1, entries 2, 8) and the bulky TIPS containing amines exhibited better *cis*-sele-

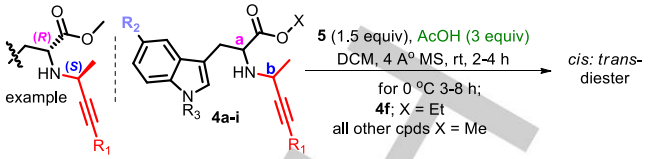


Scheme 4. Synthesis of Pictet-Spengler substrates (**4a-i**)

ctivity (compare entry 2 and 8 vs 4 and 6 in Table 1) than amines which contained a TMS- or H-substitution. Interestingly, on the other hand, when the configurations of carbon atoms **a** and **b** were opposite to each other i.e., (*R*,*S*) or (*S*,*R*), reactions were 100% *cis*-selective regardless of temperature, and size of the alkyne protecting groups (TIPS, TMS and H), as indicated by entries 1, 3, 5, 7, and 9. As expected, the P-S reaction with an electron rich tryptophan (**4f**, 5-MeO) reacted faster. The C-5 ring-A oxygen function, however, had no effect on the outcome of the diastereoselectivity other than speeding up the rate. Similarly, the same pattern was observed with the L-(-)-tryptophan derivatives (entries 8-9). More importantly, all of the diastereomers could easily be separated and the pure, isolated *cis*-diesters could be converted into the corresponding *trans*-diesters (100% *de*), simply by treatment with TFA in DCM for 2-20 hours at room temperature (see SI for details).

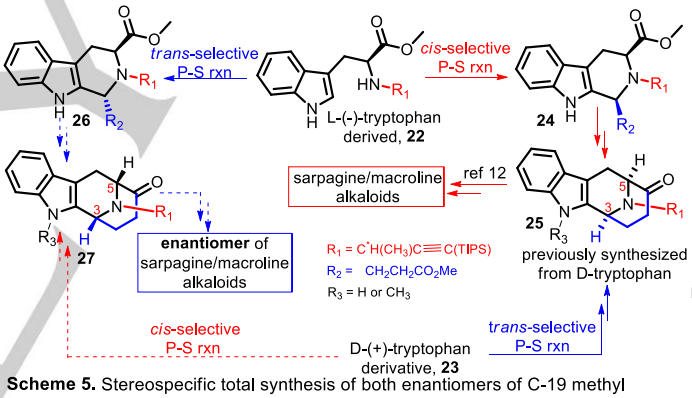
Consequently, conditions were designed for selective generation of either the *trans*- or the *cis*-diesters from either D(+)- or L(-)-tryptophans. It is well-known that plants or natural sources generally produce one enantiomer of the chiral natural products. Due to this, it is possible to isolate and screen for bioactivity only one of the enantiomers. Logically, the unnatural enantiomer might actually be as good as the natural enantiomer or even better in activity as well as in toxicity profile depending on metabolism. The development of the life-saving anti-HIV/AIDS drug emtricitabine by Professor Liotta at Emory, exemplified the tremendous potential of unnatural enantiomers of bioactive molecules in drug discovery.[15] As depicted in Scheme 5, the 3,5-*cis*-disubstitution (biogenetic numbering, **24** and **25**) of the natural enantiomer of sarpagine/macroline alkaloids could be furnished either from natural L-tryptophan via a *cis*-selective P-S reaction or alternatively from D-tryptophan via a *trans*-selective P-S reaction. Conversely, the unnatural enantiomer of these alkaloids would also be accessible either from L-tryptophan *via* a trans-selective P-S reaction (**26** and **27**) or alternatively from D-tryptophan *via* a *cis*-selective P-S reaction (see Scheme 5 for details). This novel ambidextrous approach to the synthesis of both the natural and unnatural enantiomers of bioactive sarpagine-type alkaloids would permit the rapid screening of the biological activity of both of the enantiomers. To illustrate the usefulness of this method, the synthesis of key intermediates for natural product synthesis,[12a]

Table 1. P-S reaction of amines **4a-i** with aldehyde **5**



entry	amine-substrate	R_1	R_2	R_3	a	b	*c: t* (0)[d]	*c: t* (*rt*)[e]	y[a] (%)
1	**4a**	TIPS	H	H	*R*	*S*	100:0	100:0	90
2	**4d**	TIPS	H	H	*R*	*R*	72:28	65:35	95
3	**4b**	TMS	H	H	*R*	*S*	100:0	100:0	82
4	**4e**	TMS	H	H	*R*	*R*	43:57	50:50	84
5	**4c**	H	H	H	*R*	*S*	100:0	100:0	85
6	**4i**	H	H	H	*R*	*R*	58:42[b]	-[c]	78
7	**4f**	TIPS	OMe	Me	*R*	*S*	100:0	100:0	85
8	**4g**	TIPS	H	H	*S*	*S*	82:18	72:28	85
9	**4h**	TIPS	H	H	*S*	*R*	100:0	100:0	88

[a]Isolated yields; [b]both *cis* and *trans* isomer had the same R_f, and were isolated after complete conversion into the *trans*-diester; [c]not done; *cis*: *trans* at [d]0 °C; [e]room temp.

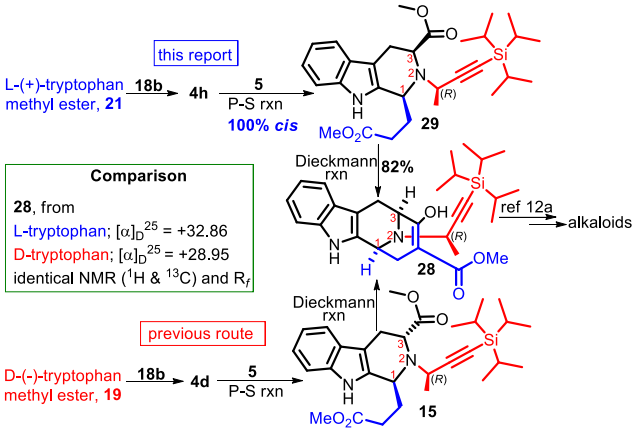


Scheme 5. Stereospecific total synthesis of both enantiomers of C-19 methyl substituted macroline/sarpagine indole alkaloids from either L-(-)- or D-(+)-tryptophan

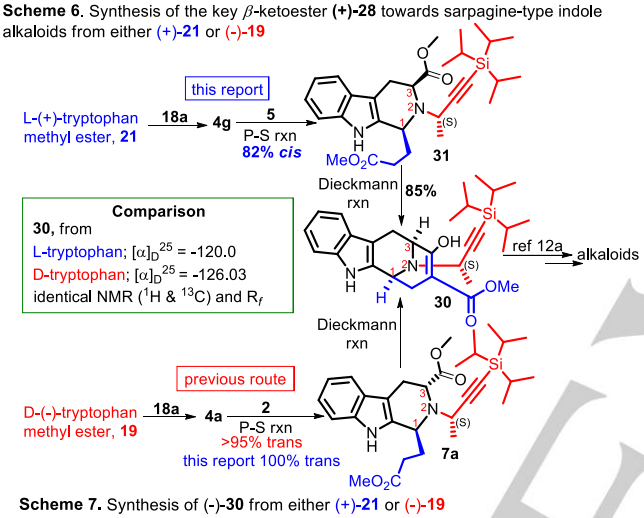
28 and **30**, starting from L-tryptophan derivative **21** were undertaken. The *β*-ketoesters **28**, and **30** are key intermediates for the total synthesis of a group of sarpagine-related indole alkaloids and were employed previously in total synthesis and were synthesized from D-(-)-tryptophan methyl ester.[12a] As shown in Scheme 6, the *cis*-diester **29** was synthesized from L-(+)-tryptophan methyl ester **21** *via* N_b-alkylation (**4h**) and the *cis*-specific P-S reaction (100% *cis*, Table 1, entry 9). The *cis*-diester **29** upon Dieckmann cyclization provided the *β*-ketoester **28** in excellent yield. The ester **28** was previously synthesized from (-)-**19**.[12a] The indoles from both routes were identical in all respects (R_f, ^{1}H NMR, and ^{13}C NMR), as well as the optical rotation (see Scheme 6, note 17, and SI). This enabled one to access the same group of indole alkaloids starting from L-tryptophan *via* the unprecedented *cis*-specific P-S reaction reported herein (Scheme 6).

Similarly, the *β*-ketoester **30** could be prepared form D-tryptophan *via* **7a** (100% *trans*-selective P-S reaction, which was >95% previously[12a]), as depicted in Scheme 7. Importantly the same *β*-ketoester **30** could be synthesized from (+)-**21** *via* a *cis*-selective

(82% *cis*) P-S reaction. The spectral properties of (-)-**30** from both (+)-**21** and (-)-**19** are identical in all respects (Scheme 7).



Scheme 6. Synthesis of the key *β*-ketoester **(+)-28** towards sarpagine-type indole alkaloids from either (+)-**21** or (-)-**19**



Scheme 7. Synthesis of (-)-**30** from either (+)-**21** or (-)-**19**

In summary, we have developed a novel strategy to gain access to the 1,2,3-trisubstituted TH*β*Cs with the required C-3/C-5 stereochemistry of a group of sarpagine-related indole alkaloids with unprecedented control of the asymmetric P-S reaction. This report also illustrates the ability to achieve the complete *cis*-selectivity of the PS reaction to form the 1,2,3-trisubstituted TH*β*C by internal asymmetric induction. Key intermediates [(+)-**28** and (-)-**30**] towards the total synthesis of a group of thirty C-19 methyl substituted alkaloids have been accessed from the natural and cheaper L-(-)-tryptophan now instead of the previously developed route from D-(+)-tryptophan. This permits the synthesis of either enantiomer from the same TH*β*C branching point.

Acknowledgements

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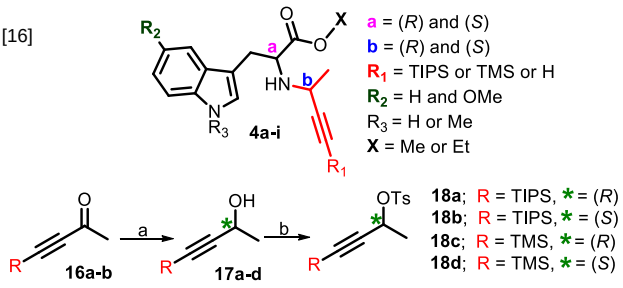

Scheme 3. Different amine-substrate for the P-S reaction and syntheis of tosylate units; Reagents and conditions: a) (*S*,*S*)-Ru or (*R*,*R*)-Ru catalyst (1 mol%), *i*-PrOH, rt, 3 h, **85-90%**; b) TsCl (2.5 equiv), Et_3N (4 equiv), DMAP (10 mol%), CH_2Cl_2, -30 °C to rt, **92-95**%.

[17]

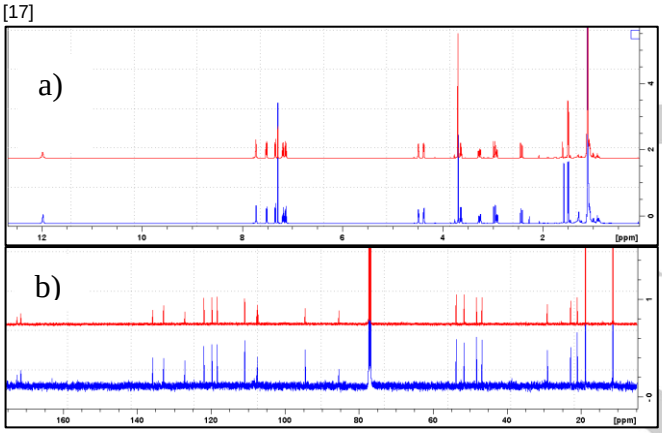

Figure 1. Comparison between the (a) ^{1}H and (b) ^{13}C NMR spectra of **(+)-28** from L-tryptophan (red) and D-tryptophan (blue) as shown in Scheme 6