An Enantioenriched Synthesis of (S)-Ketamine

**Significance:** Ketamine is an anesthetic and analgesic that has been used in both human and veterinary medicine since 1963. While commercially available as a racemic mixture, the S-enantiomer has more potent anesthetic effects while also avoiding the side effects of the R-enantiomer such as restlessness, agitation, and hallucinations. In order to access enantioenriched (S)-ketamine, the Kiyooka group developed a short synthesis that provides the desired product in 36% yield.

**Comment:** The synthesis begins with a highly selective Kiyooka aldol reaction which affords the desired enantiomer in 86% ee as a 3:2 mixture of atropisomers. After reduction and benzyl protection of the primary alcohol, the secondary alcohol reacts with trichloroacetyl isocyanate and hydrolyzes to give a carbamate. Exposure to dehydrating conditions affords an allyl cyanate which undergoes an Ichikawa rearrangement with stereochemical retention. Reduction and HCl salt formation sets the stage for the final ozonolysis which provides (S)-ketamine.

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